SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Eladynos

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dose (40 microliters) contains 80 micrograms of abaloparatide.

Each pre-filled pen contains 3 mg of abaloparatide in 1.5 mL of solution (corresponding to 2 milligrams per mL).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Colourless, clear solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of osteoporosis in postmenopausal women at increased risk of fracture (see section 5.1).

4.2 Posology and method of administration

Posology

The recommended dose is 80 micrograms once daily.

The maximum total duration of treatment with abaloparatide should be 18 months (see sections 4.4 and 5.1).

Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate.

Following cessation of abaloparatide therapy, patients may be continued on other osteoporosis therapies such as bisphosphonates.

Missed dose

If a patient forgets or cannot administer their dose at the usual time, it can be injected within 12 hours of the normally scheduled time. Patients should not administer more than one injection in the same day and should not try to make up for a missed dose.

Special populations

Elderly patients

Dose adjustment based on age is not required (see section 5.2).

Renal impairment

Abaloparatide must not be used in patients with severe renal impairment including patients with end-stage renal disease (see section 4.3). In patients with mild to moderate renal impairment, dose-based adjustment is not required (see section 5.2).

Hepatic impairment

No data are available in patients with impaired hepatic function. Dose adjustment is not required for these patients, as it is unlikely that hepatic impairment will have a significant effect on abaloparatide exposure (see section 5.2).

Paediatric population

Abaloparatide should not be used in children and adolescents less than 18 years because of safety concerns (see section 5.3).

Method of administration

For subcutaneous use only.

The first injection(s) administered by the patient or caregiver should be performed under the guidance of an appropriately qualified health care professional (see section 4.4). Patients and/or caregivers should be trained in the subcutaneous administration of abaloparatide (see section 6.6). A detailed instruction for use is included in each pack to instruct patients on the correct use of the injection pen.

Abaloparatide should be injected in the lower abdomen. The site of the injection should be rotated every day. Injections should be administered at approximately the same time every day.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Pregnancy and breast-feeding (see section 4.6)
- Women of childbearing potential (see sections 4.6 and 5.3)
- Pre-existing hypercalcaemia
- Severe renal impairment (see sections 4.2 and 5.2)
- Unexplained elevations of serum alkaline phosphatase
- Patients with known risks for osteosarcoma such as those who have received prior external beam or implant radiation therapy involving the skeleton (see section 5.3)
- Patients with skeletal malignancies or bone metastases

4.4 Special warnings and precautions for use

Orthostatic hypotension and increased heart rate

Orthostatic hypotension and transient episodes of increase in heart rate may occur with abaloparatide, typically within 4 hours of injection. Symptoms may include dizziness, palpitations, tachycardia, or nausea, and may resolve by having the patient lie down. The first injection(s) of abaloparatide should be performed under the guidance of an appropriately qualified health care professional who may observe the patient during the first hour after injection. Abaloparatide should always be administered where the patient can sit or lie down if necessary.

Abaloparatide may have vasodilating effect on vascular smooth muscle and positive chronotropic/inotropic effects on cardiac muscle. Individual benefit risk assessment is important. Blood pressure, cardiac status and ECG should be assessed prior to beginning treatment with abaloparatide.

Patients with cardiac disease should be monitored for worsening of their disease. If severe orthostatic hypotension or severe cardiovascular symptoms occur, the treatment should be discontinued.

Hypercalcaemia

In normocalcaemic patients, transient elevations of serum calcium concentrations have been observed following abaloparatide injection. Serum calcium concentrations reach a maximum at approximately

4 hours and return to baseline by 24 hours after each dose. Therefore, if blood samples for serum calcium measurements are taken, this should be done approximately 24 hours after the most recent injection.

Routine calcium monitoring during therapy is not required in patients without additional risk factors for hypercalcaemia.

Hypercalciuria and urolithiasis

Abaloparatide may cause hypercalciuria. It is unknown whether abaloparatide may exacerbate urolithiasis in patients with active or a history of urolithiasis. If active urolithiasis or pre-existing hypercalciuria is suspected, measurement of urinary calcium excretion should be considered.

Duration of treatment

The maximum total duration of treatment with abaloparatide should be 18 months. Studies in rats indicate an increased incidence of osteosarcoma with long-term administration of abaloparatide (see section 5.3).

Sodium content

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

4.5 Interaction with other medicinal products and other forms of interaction

No dedicated clinical drug-drug interaction studies have been performed with abaloparatide. The interaction potential of abaloparatide is regarded low considering its pharmacokinetic properties.

There is no data on efficacy of abaloparatide in patients with prior or concomitant bisphosphonate or glucocorticoid treatment.

Concomitant use of vasoactive medicinal products may predispose to orthostatic hypotension since the blood pressure lowering effect of abaloparatide may be increased, see section 4.4.

Sporadic case reports have suggested that hypercalcaemia may predispose patients to digitalis toxicity. Because abaloparatide has been shown to increase serum calcium, it should be used with caution in patients taking digitalis.

4.6 Fertility, pregnancy and lactation

This medicine is not indicated in women of childbearing potential. It is not to be used in women who are, or may be, pregnant or breast-feeding (see sections 4.1 and 4.3).

Pregnancy

Eladynos is contraindicated during pregnancy (see section 4.3).

Breast-feeding

It is unknown whether abaloparatide is excreted in human milk. A risk to the newborns/infants cannot be excluded. Eladynos is contraindicated during breast-feeding (see section 4.3).

Fertility

No data are available on the effect of abaloparatide on human fertility. Studies in rats with abaloparatide have shown no effects on male fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Abaloparatide has no or negligible influence on the ability to drive and use machines. Transient orthostatic hypotension or dizziness may occur following administration of abaloparatide (see

section 4.8). These patients should refrain from driving or the use of machines until symptoms have subsided.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse drug reactions in patients treated with abaloparatide in the ACTIVE study were hypercalciuria (15.6%), dizziness (11.1%), back pain (8.6%), nausea (8.5%), headache (8.5%), arthralgia (8.4%), hypertension (6.8%), injection site reaction (6.2%), and palpitations (5.6%).

Tabulated list of adverse reactions

Of patients in the abaloparatide ACTIVE study, 90.3% of the abaloparatide patients and 88.4% of the placebo patients reported at least 1 adverse event.

The adverse reactions associated with the use of abaloparatide in osteoporosis in the ACTIVE study and in postmarketing exposure are summarised in the table below. The following MedDRA convention has been used for the classification of the adverse reactions: 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 frequency not known (cannot be estimated from the available data).

Table 1 – Tabulated list of adverse reactions

Immune system disorders *Uncommon:* Hypersensitivity *Frequency not known:* Anaphylactic reaction
Metabolism and nutrition disorders *Common:* Hypercalcaemia, hyperuricaemia
Psychiatric disorders *Common:* Insomnia
Nervous system disorders *Very common:* Dizziness *Common:* Headache
Cardiac disorders *Common:* Palpitations, tachycardia
Vascular disorders *Common:* Hypertension *Uncommon*: Orthostatic hypotension
Gastrointestinal disorders *Common:* Nausea, abdominal pain, constipation, diarrhoea, vomiting *Uncommon:* Abdominal distension
Skin and subcutaneous tissue disorders

Common: Pruritus, rash
Musculoskeletal and connective tissue disorders *Common:* Back pain, arthralgia, pain in extremity, muscle spasms (back and legs), bone pain
Renal and urinary disorders *Very common*: Hypercalciuria *Common:* Nephrolithiasis
General disorders and administration site conditions *Common:* Injection site reaction, fatigue, asthenia, malaise *Uncommon*: Pain

Description of selected adverse reactions

Increased heart rate

In the QT study, the placebo-adjusted mean heart rate increase was 14.5 beats per minute (bpm)

15 minutes after administration. This increase in heart rate was most prominent during the first hour post dose but was seen up to 6 hours in some subjects.

In the ACTIVE study, heart rate was measured one hour post dose of every study visit, with median heart rate increase from pre-dose of 14 bpm in abaloparatide treated patients as compared to 7 bpm in placebo treated patients. Patients with >20 bpm increase in heart rate at 1 hour after the first dose were more likely to experience palpitations and/or increases in heart rate >20 bpm during subsequent treatment. Adverse reactions of tachycardia and sinus tachycardia were reported in 1.6% of patients receiving abaloparatide and 0.4% of patients in the placebo group.

Orthostatic hypotension

In women with postmenopausal osteoporosis, adverse reactions of orthostatic hypotension were reported in 1% of patients receiving abaloparatide and 0.6% of patients in the placebo group.

Injection site reactions

Abaloparatide can cause injection site reactions including injection site bruising, erythema, haemorrhage, hypersensitivity, pain, rash, and swelling. The overall incidence in the abaloparatide arm was 5.3% compared to 4.0% in the placebo group.

Laboratory findings

Serum calcium

Abaloparatide can cause transient increases in serum calcium levels measured 4 hours post-dose. The overall incidence of hypercalcaemia, defined as albumin-corrected serum calcium ≥2.67 mmol/L (or

≥10.7 mg/dL) in the abaloparatide arm was higher (3.3%) compared to the placebo group (0.4%).

Serum uric acid

Abaloparatide increased serum uric acid concentrations. In the ACTIVE study, 25% of patients in the abaloparatide group had normal baseline uric acid concentrations which were increased above the normal range at post-baseline, compared with 5% in the placebo group.

Hypercalciuria and urolithiasis

In the clinical trial of women with postmenopausal osteoporosis, the overall incidence of urine calcium: creatinine ratio >0.00113 mmol/µmol (or >400 mg/g) was higher with abaloparatide than with placebo (20% vs 15%, respectively). Urolithiasis was reported in 1.4% of abaloparatide-treated patients and 1.2% of placebo-treated patients.

Immunogenicity

Of the patients receiving abaloparatide for 18 months, 42.9% developed anti-abaloparatide antibodies and 28.5% developed *in vitro* neutralising antibodies. Formation of anti-abaloparatide antibodies is associated with increased clearance of abaloparatide. These changes in clearance could be related to anti- abaloparatide antibodies interfering with the accurate measurement of abaloparatide plasma concentrations. Compared to antibody negative patients, no clinically relevant differences in safety or efficacy were observed for patients who were antibody positive or who were positive for *in vitro* neutralising antibodies.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/

4.9 Overdose

Signs and symptoms

In clinical trials, abaloparatide has been administered subcutaneously in single doses of up to

320 micrograms and in repeated doses of up to 120 micrograms/day for 7 days. The primary dose-limiting adverse effect was postural dizziness.

The effects of overdose that might be expected include transient hypecalciuria, hypercalcaemia, nausea, vomiting, dizziness, palpitations, orthostatic hypotension and headache.

In the clinical programme with an earlier pen design, accidental overdose was reported in a patient who received 400 micrograms in one day (5 times the recommended clinical dose). The

patient experienced asthenia, headache, nausea, and vertigo. Serum calcium was not assessed on the day of the overdose, but on the following day the patient's serum calcium was within the normal range.

Overdose management

There is no specific antidote for abaloparatide. Treatment of suspected overdose may include transitory discontinuation of treatment, monitoring of serum calcium and implementation of appropriate supportive measures, such as hydration.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Calcium homeostasis, parathyroid hormones and analogues, ATC code: H05AA04

Mechanism of action

Abaloparatide is a 34 amino acid peptide that shares 41% homology to parathyroid hormone [PTH(1-34)] and 76% homology to parathyroid hormone related peptide [PTHrP(1-34)], and is an activator of the PTH1 receptor signalling pathway. Abaloparatide stimulates new bone formation on trabecular and cortical bone surfaces by stimulation of osteoblastic activity.

Abaloparatide causes transient and limited increases in bone resorption and increases bone density.

Clinical efficacy and safety

The efficacy and safety of once daily abaloparatide was evaluated in a randomised, multicentre, double- blind, placebo- and open-label active comparator-controlled (teriparatide) clinical study (ACTIVE study) for 18 months of treatment with 1 month follow-up in 2 070 postmenopausal women aged 50 to 86 years (mean age of 69; 15% were <65 years of age, 65% were 65 to <75 years of age, and 20% were ≥75 years of age) who were enrolled and randomised to receive abaloparatide 80 micrograms (N=696), placebo (N=688), or 20 micrograms teriparatide (N=686). Approximately 76% of patients were Caucasian, 19% were Asian, and 4% were Black. Of the total study population, 28% were Hispanic. Women took daily supplemental calcium (500 to 1 000 mg) and vitamin D (400 to 800 IU) per day. The primary endpoint in ACTIVE was the incidence of new vertebral fractures in abaloparatide-treated patients versus placebo.

At baseline, the mean T-scores were -2.9 at the lumbar spine, -2.2 at the femoral neck, and -1.9 at the total hip. At baseline, 42% of patients had no prior fracture, 23% of patients had at least one prevalent vertebral fracture, and 43% had at least one prior non-vertebral fracture.

Effect on new vertebral fractures

In the ACTIVE study at 18 months, abaloparatide and teriparatide significantly reduced the absolute risk of new vertebral fractures versus placebo in postmenopausal patients with osteoporosis (p<0.0001; see Table 2).

Table 2 – ACTIVE Trial: the effect* of abaloparatide on the risk of new vertebral fracture at 18 months

Parameter	PBO (N=600)	ABL (N=583)	TER (N=600)
Number of women with vertebral fracture, n (%)	25 (4.2)	3 (0.5)	4 (0.7)
Absolute risk difference vs placebo† (%) (95% CI)	n/a	3.7 (2.0, 5.6)	3.5 (1.8, 5.5)

*Based on Modified Intent to Treat Population (patients with baseline and post-baseline spine radiographs).
†Absolute risk difference was calculated as (PBO – ABL) and (PBO – TER). PBO=placebo, ABL=abaloparatide, TER=teriparatide, CI=confidence interval

Effect on non-vertebral fractures

In the ACTIVE study at 19 months, the incidence of non-vertebral fractures was similar between the abaloparatide (2.7%) and teriparatide (2.0%) groups, and not statistically different compared to placebo (3.6%) (see Table 3).

Table 3 – ACTIVE Trial: time-to-event of non-vertebral fracture at 19 months

Parameter	PBO (N=688)	ABL (N=696)	TER (N=686)
K-M estimated event rate (%) (95% CI)	3.6 (2.3, 5.4)	2.7 (1.6, 4.4)	2.0 (1.1, 3.4)
Number of patients with event n (%)	21 (3.1)	15 (2.2)	12 (1.7)
Absolute risk difference vs placebo* (%) (95% CI)	n/a	0.9 (-1.1, 2.9)	1.6 (-0.3, 3.5

*Absolute risk difference was calculated as (PBO – ABL) and (PBO – TER).
PBO=placebo, ABL= abaloparatide, TER=teriparatide, K-M=Kaplan Meier, CI=confidence interval

Effect on bone mineral density (BMD)

In the ACTIVE study, abaloparatide significantly increased BMD at all anatomical sites measured, versus placebo at 6, 12 and 18 months. The mean percent change in BMD at 18 months was 9.1% vs 0.5% at the lumbar spine, 3.3% vs 0% at the total hip, and 2.7% vs -0.4% at the femoral neck for abaloparatide versus placebo groups, respectively (all p<0.0001). At the ultra-distal radius, the mean percent change in BMD at 18 months was 1.2% vs -1.0% for abaloparatide versus placebo groups.

Abaloparatide demonstrated consistent increases in BMD measurements regardless of age, years since menopause, race, geographic region, presence or absence of prior fracture (vertebral, non-vertebral), severity of disease, and BMD at baseline.

Bone turnover markers

In postmenopausal women with osteoporosis, the bone anabolic marker (s-PINP) showed a 90% increase above baseline at 1 month, and this effect was sustained throughout the abaloparatide treatment period. The bone resorption marker (s-CTX) showed no increase at 1 month, and a transient 22% increase above baseline at 3 months that returned to baseline at the end of treatment.

Post treatment management

Extension study

Upon completion of the ACTIVE trial, 963 patients, enrolled in the ACTIVExtend trial, an open-label extension study, where all patients received up to 24 months of treatment with 70 mg alendronate (ALN) weekly and calcium and vitamin D supplements. This included 494 patients who had previously received placebo and 469 patients who had previously received abaloparatide. Patients who received teriparatide during the ACTIVE trial were not eligible to participate in the ACTIVExtend trial. Results for vertebral fracture risk reduction at 43 months since randomisation are presented in Table 4.

Effect on new vertebral fractures – Extension study

In the ACTIVExtend study at 43 months, abaloparatide/ALN significantly reduced the absolute risk of new vertebral fractures vs placebo/ALN ($p<0.0001$; see Table 4). Teriparatide followed by alendronate has not been studied.

Table 4 – ACTIVExtend trial: the effect* of abaloparatide/ALN on the risk of new vertebral fracture at 43 months†

Parameter	PBO/ALN (N=489)	ABL/ALN (N=457)
Number of women with vertebral fracture, n (%)	26 (5.3)	4 (0.9)
Absolute risk difference vs placebo/ALN‡ (%) (95% CI)	n/a	4.4 (2.3, 6.9)

*Based on Modified Intent to Treat Population (patients with baseline and post-baseline spine radiographs).
†Alendronate started at 19 months
‡Absolute risk difference was calculated as (PBO/ALN – ABL/ALN). PBO=placebo, ABL=abaloparatide, ALN=alendronate, CI=confidence interval

Effect on non-vertebral fractures – Extension study

In the ACTIVExtend study at 43 months, abaloparatide/ALN numerically reduced the risk of non-vertebral fractures versus placebo/ALN. The incidence of non-vertebral fractures with abaloparatide/ALN (4.2%) was not statistically different compared to placebo (6.7%) (see Table 5).

Table 5 – ACTIVExtend trial: time-to-event of non-vertebral fracture at 43 months*

Parameter	PBO/ALN (N=494)	ABL/ALN (N=469)
K-M estimated event rate (%) (95% CI)	6.7 (4.8, 9.3)	4.2 (2.7, 6.4)
Number of patients with event n (%)	32 (6.5)	19 (4.1)
Absolute risk difference vs placebo/ALN† (%) (95% CI)	n/a	2.5 (-0.4, 5.4)

*Alendronate started at 19 months

† Absolute risk difference was calculated as (PBO/ALN – ABL/ALN).

PBO=placebo, ABL=abaloparatide, ALN=alendronate, K-M=Kaplan Meier, CI=confidence interval

Effect on bone mineral density (BMD) – Extension study

The mean percent change in BMD through 43 months was 14.7% vs 6.8% at the lumbar spine, 6.3% vs 2.9% at the total hip, 5.0% vs 1.6% at the femoral neck, and 1.1% vs 1.1% at the ultra-distal radius for abaloparatide/ALN versus placebo/ALN groups, respectively.

Paediatric population

See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption

The median (range) time to peak concentration of abaloparatide 80 micrograms was 0.5 h (0.25 to 0.52 h) following subcutaneous administration. The absolute bioavailability of abaloparatide in healthy subjects after subcutaneous administration of 80 micrograms dose was about 39%.

Distribution

The *in vitro* plasma protein binding of abaloparatide was approximately 70%. The volume of distribution was approximately 45 L.

Biotransformation

No specific metabolism or excretion studies have been performed with abaloparatide. The metabolism of abaloparatide is consistent with non-specific proteolytic degradation into smaller peptide fragments, followed by elimination by renal clearance. *In vitro* studies showed that abaloparatide, at clinically relevant concentrations, does not inhibit or induce Cytochrome P450 enzymes.

Elimination

The mean apparent total plasma clearance for subcutaneous administration is 168 L/h in healthy subjects, and the mean half-life of abaloparatide is about 1 h. The peptide fragments are primarily eliminated through renal excretion. Active secretion of abaloparatide in the kidneys cannot be ruled out.

Abaloparatide is not a substrate of the renal transporters P-gp, OAT1, OAT3, OCT2, MATE1 or MATE2K. Furthermore, abaloparatide does not inhibit P-gp, BCRP, OAT1, OAT3, OCT2, OATP1B1 and OATP1B3 transporters *in vitro* at its clinically relevant concentrations.

Linearity

Abaloparatide systemic exposure was generally increasing with the increase of its subcutaneous doses from 5 micrograms up to 240 micrograms. There was a general tendency towards less than dose- proportional increases, and no further increase in abaloparatide systemic exposure was observed as its dose increased to 280 micrograms and 320 micrograms.

Renal impairment

Abaloparatide exposure increased with decreasing CrCl. Subjects with mild, moderate and severe renal impairment had Cmax increases of 3%, 28% and 44%, respectively, and AUC increases of 17%, 68% and 113%, respectively, compared to subjects with normal renal function (see sections 4.2 and 4.3).

No studies have been performed in patients undergoing dialysis for chronic renal failure.

Hepatic impairment

No studies have been performed in patients with hepatic impairment. Abaloparatide is a peptide and not an inhibitor or an inducer of hepatic drug metabolising enzymes. The elimination is through proteolytic degradation and renal excretion, and it is unlikely that hepatic impairment will have any significant effect on abaloparatide exposure. No dose adjustment is needed for these patients (see section 4.2).

Elderly

No age related differences in abaloparatide pharmacokinetics were detected during clinical studies, including postmenopausal women ranging from 49 to 86 years of age.

5.3 Preclinical safety data

In a 2-year rat carcinogenicity study, abaloparatide displayed an increase in the overall incidence of osteosarcomas at doses that were 4 times higher than the systemic exposure observed in humans following a subcutaneous dose of 80 micrograms based on AUC comparisons. Neoplastic changes related to the treatment with abaloparatide consisted of dose-dependent increased incidence of osteosarcomas and osteoblastomas. The incidence and earliest occurrence of tumours was similar in both male and female rats. The relevance of these rat findings to humans is uncertain, thus the use of abaloparatide should be avoided for patients at increased risk of osteosarcoma.

In toxicology studies in rats and monkeys, findings included soft tissue mineralization at doses that were approximately 2 and 3 times, respectively, the exposure in humans at daily subcutaneous doses of 80 micrograms.

Subcutaneous administration of abaloparatide at doses that were approximately 0.3, 2.4 and 3.8 times the exposure in humans at daily subcutaneous doses of 80 micrograms to the conscious dog produced a dose- dependent transient increase in heart rate lasting approximately 3 hours, had marginal effects on mean arterial blood pressure. Additionally, abaloparatide had marginal effects on the QTc interval, with a non- significant tendency towards a decrease in QTc with increasing dose, which is consistent with its minimal effects on hERG potassium currents and Purkinje fibres at clinically relevent concentrations.

Abaloparatide was not genotoxic or mutagenic in a standard battery of tests.

No embryofoetal development or pre/postnatal development studies have been conducted in female animals because the intended population for abaloparatide is postmenopausal women. Effects on male fertility were evaluated in rats, and no impact on male fertility was observed at doses 27 times the exposure in humans at daily subcutaneous doses of 80 micrograms.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Acetic acid (for pH adjustment)
Sodium acetate trihydrate (for pH adjustment)
Phenol
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the package materials.

6.4 Special precautions for storage

Store in a refrigerator (2 °C–8 °C). Do not freeze.
After first use or once removed from the refrigerator, store the pen below 25 °C.
It must be used within 30 days.

6.5 Nature and contents of container

Cartridge (siliconised Type I glass) with a plunger (chlorobutyl rubber), crimp cap (bromobutyl rubber seal)/aluminium assembled into a disposable pen.
Eladynos is available in pack sizes of 1 or 3 pre-filled pens.
Each pre-filled pen contains 1.5 mL of solution (30 doses).
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Each pen should be used by only one patient. A new, sterile needle must be used for every injection. The pen should only be used with 8 mm, 31-gauge needles. No needles are supplied with the medicinal product. Do not store the pen with the needle attached.
Eladynos should not be used if the solution is cloudy, coloured or contains particles.
Before using the pen device for the first time, the patient should read and understand the instructions on how to use the pen. A detailed Instructions for Use is provided with the pen in the carton.

Injecting Eladynos

Step 1 Check the Eladynos pen • Before using the pen always check the label to be sure it is the correct pen. • Make note of the date of Day 1 in the space provided on the carton. Do not use the pen for more than 30 consecutive days. **Dispose of the pen 30 days after first use.** • Pull off the pen cap from the pen. • **Check the Eladynos cartridge.** The liquid should be clear, colourless, and free of particles; if not, do not use. Small air bubbles may be present in the liquid; this is normal.
Step 2 Attach needle to the Eladynos pen • Remove the protective paper from a new needle. • **Push the capped needle straight** onto the pen and **twist until it is secure**. Make sure the needle is straight so that it doesn't bend when inserting. The pen will not work if the needle is not properly attached. Do not over-tighten as this may make the needle difficult to remove. • Pull off the **outer needle cap** from the needle and keep it to use after the injection. • Carefully pull off the **inner needle cap** and dispose of it.
Step 3 Day 1 Only – Testing an Eladynos pen prior to first injection • The pen has medicine for 30 days and a small amount to test each pen once, to confirm it is working properly. • **Attention:** If the patient tests the pen before every injection, then the pen will run out of medicine early. **Therefore, perform Step 3 once for each pen, only on Day 1, prior to first injection.** • For **Day 2 through Day 30**, do not test the pen again, **go directly to Step 4 to set the dose for the injection.**

• **Turn the dose knob** on the pen away from you (clockwise) until it stops. **"•80" will be lined up** in the dose display window.
• **Hold the pen with the pen needle pointing up.**
• **Press the green injection button** until it will not go any further. **Liquid, as a drop or stream, come out of the needle tip.** If no liquid appears, see Troubleshooting in the "Instructions for use" at the end of the package leaflet.
"●0" will be lined up in the dose display window.

Step 4 Set the dose on the Eladynos pen
• **Turn the white knob** on the pen away from you (clockwise) until the knob stops and
"●80" is lined up in the display window. The pen is now ready for injection.

Step 5 Choose and clean the injection site
• Injections should be given in the lower abdomen. Avoid the 5 cm area around your belly button (navel).
• For each injection, select a different injection site on the abdomen each day. Only inject into clear skin. Do not inject into areas on the abdomen where the skin is tender, bruised, red, scaly, or hard. Avoid areas with scars or stretch marks.
• **Wipe the injection site with an alcohol swab** and allow it to dry.
• Do not touch, fan, or blow on the injection site after it has been cleaned.
• Note: It may be recommended to pinch up the skin at the site where the injection will occur. Once the needle enters the skin, the pinch can be released.

Step 6 Giving your Eladynos pen injection
• **Insert the needle** straight into your skin.
• **Press and HOLD the green button until ALL** events below are complete and "●0" **is displayed**.
• Hold for 10 seconds to give full dose, **withdraw pen from skin**, and THEN **release the button.**

Step 7 Remove the pen needle
• Carefully **place the outer needle cap back on the needle**. Then carefully press on the outer needle cap until it snaps into place and is secure.
• **Unscrew the capped needle** (like unscrewing a cap from a bottle). To unscrew the capped needle, squeeze the cap at the base against the needle and turn it 8 or more turns and then gently pull until the capped needle comes off.
• Note: Do not push down on the outer needle cap while unscrewing the needle.
• Note: You should see a gap widening between the outer needle cap and the pen as you unscrew the needle.

Step 8 After your injection
• Firmly **replace the pen cap** onto the pen.
• Keep the pen cap on your Eladynos pen between injections.
• The patient may have slight bleeding, this is normal. Do not rub the injection site. If slight bleeding occurs, press a cotton ball or gauze pad as needed to stop the bleeding. The patient may also cover the injection site with a small adhesive bandage.

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

7. MARKETING AUTHORISATION HOLDER

Rafa Laboratories Ltd.
P.O.B 405, Jerusalem 9100301
Israel

8. MARKETING AUTHORISATION NUMBER

181-72-38588

9. DATE OF APPROVAL

March 2026.