Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) – 1986
This medicine is dispensed with a doctor's prescription only

Lecigon
Intestinal gel

Active ingredients
Each 1 ml of gel contains:
- 20 mg levodopa
- 5 mg carbidopa monohydrate
- 20 mg entacapone

Inactive ingredients and allergens in this medicine: see section 2 under 'Important information about some of this medicine's ingredients', and section 6 'Additional information'.
Read the entire leaflet carefully before you start using this medicine. This leaflet contains concise information about this medicine. If you have any further questions, consult your doctor or pharmacist.
This medicine has been prescribed to treat your illness. Do not pass it on to others. It may harm them, even if it seems to you that their illness is similar to yours.

1. What is this medicine intended for?

Lecigon is used to treat advanced Parkinson's disease with severe motor fluctuations and hyperkinesia or dyskinesia when oral combinations (medicines taken by mouth) of Parkinson medication have not achieved satisfactory results.

Therapeutic group: Parkinson medicines; dopa and dopa derivatives.

Lecigon is a gel for continuous delivery that is supplied through a pump and tube directly into your small intestine.

How Lecigon works
In a person with Parkinson's disease, the levels of dopamine in the brain are low. Levodopa is converted into dopamine in the brain, thereby relieving the symptoms of Parkinson's disease. Carbidopa and entacapone improve the effect that levodopa has on Parkinson's disease.

2. Before using this medicine

Do not use this medicine if:

- you are sensitive (allergic) to the active ingredients (levodopa, carbidopa, entacapone) or any of the other ingredients in this medicine (see section 6).
- you have an eye problem called narrow-angle glaucoma (an acute type of glaucoma).
- you have severe heart failure.
- you have severely irregular heartbeat (arrhythmia).
- you recently had a stroke.
- you have a serious liver disease.
- you are taking medicines for depression called selective MAO-A inhibitors (like moclobemide) and non-selective MAO inhibitors (like phenelzine). Treatment with these medicines must be discontinued at least two weeks before starting treatment with Lecigon. See also below under 'Interactions with other medicines'.
- you have a tumour of the adrenal gland that causes overproduction of adrenaline and noradrenaline (pheochromocytoma).
- your body produces too much cortisol (Cushing's syndrome).
- your thyroid hormone levels are too high (hyperthyroidism).

- you have ever had neuroleptic malignant syndrome (a serious, rare reaction that can occur when being treated with or stopping use of certain medicines).
- you have ever had rhabdomyolysis (a severe, rare muscle condition that affects the kidneys).
- you have ever had skin cancer, or you have any unusual moles or marks on your skin which have not been looked at by your doctor.

Special warnings about using this medicine
Talk to your doctor before using Lecigon if you have or ever have had:
- a heart attack or any other cardiovascular disease, including angina and irregular heartbeat.
- asthma or any other lung problem.
- a kidney or liver disease.
- a hormone problem.
- a stomach ulcer.
- Convulsions.
- a serious psychological issue, like psychosis.
- an eye problem called wide-angle glaucoma.
- surgery on the upper part of your stomach.
- polyneuropathy or a medical condition associated with polyneuropathy. Progressive weakness, pain, numbness or loss of sensation in the fingers or feet (symptoms of polyneuropathy) have been reported in patients who received intestinal gel that contains levodopa/carbidopa. Your doctor will check for the signs and symptoms of polyneuropathy before you start therapy with Lecigon and periodically thereafter.

Contact a doctor immediately if you experience any of the following symptoms during your treatment with Lecigon:
- **Neuroleptic malignant syndrome:**
  a serious medical condition with a combination of muscle stiffness, cramps, shaking, sweats, fever, rapid pulse, severe blood pressure fluctuations, acting out, confusion, loss of consciousness.
- **Rhabdomyolysis:**
  a serious medical condition that includes unexplained muscle pain, muscle cramps or muscle weakness. Rhabdomyolysis can be caused by neuroleptic malignant syndrome. For more information about neuroleptic malignant syndrome and rhabdomyolysis, see section 3 ‘If you stop or lower your dose of Lecigon’ and section 4 ‘Side effects’.
- **Problems from the tube or from the surgery:**
  stomach pain, nausea or vomiting. This may be due to serious problems caused by the tube or the surgery, e.g. blockage, wound or damage in the intestine.

Contact a doctor immediately if you experience any of the following symptoms <u>during your treatment</u> with Lecigon:
- You feel **depressed**, have **suicidal thoughts** or if you or other people notice any **mental changes**.
- You notice any **unusual birthmarks** or moles on your skin that have suddenly appeared or have gotten worse.
- You develop **involuntary movements** (dyskinesia). If you have not been treated with entacapone (one of the active substances in Lecigon) previously, these symptoms may be because entacapone increases the effects of levodopa and carbidopa (other active substances in Lecigon). The doctor may need to reduce your dose.
- You feel that **your treatment has become suddenly or gradually less effective**, for example your movements are difficult or slow (bradykinesia). This could be because the tube has slipped out of position in the small intestine or is blocked. It could also be because the pump is not working properly.
- You develop **diarrhoea**. It may be necessary to monitor your weight to avoid any significant weight loss, or it may be necessary to discontinue the treatment. Prolonged

or persistent diarrhoea may be a sign of inflammation in the intestine. If this happens, your doctor will need to evaluate your treatment with Lecigon.
- You experience a **loss of appetite** that worsens over time, **a feeling of weakness** and **weight loss** within a short period of time. A general medical examination, including a liver function check, may be required.

If you are unable to manage the pump and tube, you must get help from a caregiver (e.g. nurse or family member) to avoid complications (problems).

Impulse control disorders – changes in behaviour
Tell your doctor if you, your family or carer notices that you are developing urges or cravings to behave in ways that are unusual for you, or you cannot resist the impulse, drive or temptation to perform certain activities that could harm you or others. These behaviours are called 'impulse control disorders' and can include addictive gambling, excessive eating or spending, abnormally high sex drive or an increase in sexual thoughts or feelings.
Your doctor may need to adjust your dose or discontinue your treatment. For more information, see section 4 'Side effects'.

Dopamine dysregulation syndrome
Tell your doctor if you or your family/carer notices you are developing addiction-like symptoms leading to a craving for larger and larger doses of Lecigon and other medicines used to treat Parkinson's disease.

Lecigon and cancer
Lecigon contains hydrazine, which forms when carbidopa (an active substance of Lecigon) is broken down. Hydrazine can cause damage to your genes, which could lead to cancer. However, it is not known if the amount of hydrazine produced when taking the recommended dose of Lecigon can cause damage or disease.

Surgery
Before undergoing any operation, including dental surgery, let your doctor or dentist know that you are using Lecigon.

Children and adolescents
Lecigon must not be given to children or adolescents under 18 years of age.

Tests and follow-up
With long-term treatment with Lecigon, your doctor may need to perform regular checks of your liver and kidney function, blood counts, heart and blood vessels, and examine your skin to detect any skin changes. The active substances levodopa and carbidopa may cause misleading results in urine analyses. Let a medical staff member know that you are using Lecigon if you are asked to perform a urine analysis.

Interactions with other medicines
If you are taking or have recently taken other medicines, including non-prescription medicines and dietary supplements, tell your doctor or pharmacist.
Do **not** use Lecigon if you are taking:
- medicines for depression called selective MAO-A inhibitors (like moclobemide) and non-selective MAO inhibitors (like phenelzine). Treatment with these medicines must be discontinued at least two weeks before starting treatment with Lecigon.

Lecigon may increase the effect and side effects of other medicines, and other medicines may increase the effect and side effects of Lecigon. Let your doctor know if you are taking:
- medicines for depression called tricyclic medicines (like amitriptyline, clomipramine, and nortriptyline). Other types of antidepressant medicines may also affect or be affected by Lecigon.

- medicines for Parkinson's disease called selective MAO-B inhibitors (like selegiline), amantadine and dopamine agonists (like piribedil) and anticholinergics (like biperide).
- medicines for urinary incontinence (like oxybutynin), asthma and chronic obstructive pulmonary disease, COPD (like ipratropium and tiotropium). These medicines are known as anticholinergics.
- some asthma and allergy medicines (like salbutamol and terbutaline) and adrenaline. These medicines are known as sympathomimetics.
- medicines to reduce blood pressure (called antihypertensives). Using these medicines and Lecigon at the same time could cause a blood pressure drop when you stand up from sitting or lying down. It may be necessary to adjust the dose of your antihypertensive medicines.
- warfarin (a medicine to prevent blood clots). If you are being treated with Lecigon, or start, end or change your treatment with Lecigon, the effect of warfarin should be checked.

Some medicines can reduce the effect of Lecigon. Let your doctor know if you are taking:
- any iron product that is taken by mouth (tablets, capsules, solution). Iron can impair the absorption of levodopa from the gastrointestinal tract (and vice versa). You should therefore take Lecigon and your iron supplement at least 2–3 hours apart. If you do not use your pump at night, you can take the iron supplement before going to bed.
- medicines for psychosis [like phenothiazines, butyrophenones (e.g. haloperidol) and risperidone].
- medicines for nausea (like metoclopramide).
- medicines for epilepsy (like clonazepam and phenytoin).
- medicines for anxiety and sleeping pills, known as benzodiazepines (like diazepam, oxazepam and nitrazepam).
- medicines for tuberculosis (isoniazide).
- medicines for gastrointestinal cramps (papaverine).

Using this medicine and food
Lecigon is not absorbed well if taken immediately after eating protein-rich foods (like meat, fish, dairy products, nuts and seeds). Talk to your doctor if you eat a protein-rich diet.

Pregnancy and breastfeeding
If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Pregnancy
Lecigon is not recommended during pregnancy or to women of childbearing potential not using contraception unless the doctor determines that the benefits for the mother outweigh the possible risks to the foetus.

Breastfeeding
Levodopa and possibly levodopa metabolites pass into breast milk.
It is unknown whether carbidopa and entacapone or their metabolites pass into breast milk.
There is insufficient information on the effects of levodopa, carbidopa, and entacapone or their metabolites in new-borns/infants.
Therefore, you should not breastfeed while being treated with Lecigon.

Driving and using machines
Lecigon can greatly affect your ability to drive and use machines. Do not drive or use machines until you are sure how Lecigon affects you.

- Lecigon may make you feel very sleepy, or you may sometimes find yourself suddenly falling asleep (sleep attacks).

- Lecigon may cause your blood pressure to drop, such as when you stand up from sitting or lying down, and could make you feel dizzy.

Wait until you feel fully awake again or you no longer feel dizzy before driving, using tools or machines, or performing activities where lack of concentration may put you or others at risk.

Important information about some of this medicine's ingredients
Lecigon contains sodium. This medicine contains 166 mg sodium (main component of cooking/table salt) in each cartridge. This is equivalent to 8.3% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use this medicine?

Always use this medicine according to your doctor's instructions. Check with your doctor or pharmacist if you are not sure about your dose or about how to take this medicine. Only your doctor will determine your dose and how you should take this medicine.
How Lecigon is given
Lecigon is a gel that travels through a portable pump (Crono LECIG) and tube directly into the upper part of your intestine. The gel is found in the cartridge connected to the pump. The pump is connected to a tube that has been surgically positioned in your intestine via the abdominal wall.

The pump provides you a small dose throughout the day. This means that the level of the medicine in your blood stays the same. It also means that some side effects, like those affecting movement, are milder compared to medicines taken by mouth.

Before the tube is inserted into your small intestine, the doctor may choose to check whether treatment with Lecigon works for you. In such cases, the gel is given via a tube that passes through your nose, throat and stomach to your small intestine.
A manual with instructions for using the pump is supplied with the pump.
Dosage
The doctor adjusts the doses to you individually based on previous medication. It may be necessary to fine-tune the dose during the first few weeks of treatment.
Do not exceed the recommended dose.

A larger dose (called a bolus dose) is usually given in the morning when treatment is started so the blood reaches the right levels of medicine quickly. After this, a continuous maintenance dose is given during your waking hours (usually about 16 hours). If necessary, your doctor can decide to give Lecigon up to 24 hours a day.

Extra doses can be given as needed. Some people may need to increase or decrease their maintenance dose during the day. How and when you take the extra doses or adjust the dose during the day will be decided by your doctor after consulting with you.

The total daily dose, including morning dose (bolus dose), maintenance dose, and extra doses may not exceed 100 ml (which corresponds to 2000 mg levodopa, 500 mg carbidopa and 2000 mg entacapone).

If the user has dementia, the doctor may decide that the pump may only be handled by a healthcare professional or relative. The pump can be locked to prevent the daily recommended dose from being exceeded accidentally.

Opened cartridge:
The medicine cartridge is for single use only, and must not be used for longer than 24 hours, even if there is medicine left. The dosing pump with installed cartridge can be worn close to the body for up to 16 hours. During overnight treatment, the pump should not be worn next to

the body but can, for example, be kept on the bedside table. If there was a break in treatment during the night, you can continue using the opened cartridge the next day, but only for up to 24 hours after it was first opened. Do not remove the cartridge from the pump until you are finished using it (i.e. either after 24 hours have passed since it was opened or when it is empty, whichever occurs first).

The gel may become slightly yellow/reddish towards the end of its shelf life. This does not impact the effect of the treatment.

If you use more Lecigon than you need
Talk to your doctor if you experience any signs of overdose.

Signs of overdose can include:
- twitching or cramping in your eyelids that make it hard to open your eyes.
- involuntary, persistent muscle contractions that lead to repeated twisting movement or abnormal body position (dystonia).
- involuntary movements (dyskinesia).
- unusually fast, slow or irregular heartbeat.
- confusion or worrying/restlessness.
- discolouration of the skin, tongue, eyes, or urine.

If you forget to use Lecigon
Start the pump as prescribed as soon as possible. Do not increase the dose to compensate for the forgotten dose.

If you stop or lower your dose of Lecigon
Do not stop taking Lecigon or lower your dose without discussing this first with your doctor.

This is because suddenly lowering your dose or stopping treatment with Lecigon too quickly could lead to serious conditions called neuroleptic malignant syndrome and rhabdomyolysis. There is a great risk of these conditions occurring if you are being treated with a medicine for a serious psychological problem at the same time. For more information on these conditions, see section 4 ‘Side effects’.

If treatment is discontinued, you will receive another treatment instead. If treatment with Lecigon is being discontinued permanently, the tube will be removed, and the wound will be allowed to heal.

Do not take medicines in the dark! Check the label and dose <u>every time</u> you take medicine. Wear glasses if you need them.
If you have any further questions about using this medicine, consult your doctor or pharmacist.

4. <u>Side effects</u>

As with any medicine, using Lecigon may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them.
To reduce the risk of side effects, it is important for the dose of the medicine to be adjusted individually using the appropriate pump settings.

<u>Serious side effects of Lecigon</u>
Contact a doctor immediately if you experience any of the following symptoms during your treatment with Lecigon – you may need urgent medical treatment:

- itching, hives, swelling of the face, lips, tongue or throat, which may make it difficult to breathe or swallow; drop in blood pressure. These could be a sign of a severe **allergic reaction** (rare side effect).

- a combination of muscle stiffness, cramps, shaking, sweats, fever, rapid pulse, severe blood pressure fluctuations, acting out, confusion, loss of consciousness. These can be symptoms of a serious condition called **neuroleptic malignant syndrome** (*affects an unknown number of users*).

- unexplained muscle pain, muscle cramps or muscle weakness which may be a sign of **rhabdomyolysis**, a severe, rare muscle disorder in which the breakdown of muscle cells can severely affect the kidneys [frequency not known (*cannot be estimated from the available data*)]. Rhabdomyolysis can be caused by neuroleptic malignant syndrome.

  For more information about neuroleptic malignant syndrome and rhabdomyolysis, see section 3 'If you stop or lower your dose of Lecigon'.

- stomach pain, nausea, or vomiting. This may be due to **serious problems caused by the tube or the surgery**, such as blockage, wound or damage in the intestine *(common side effect*).

- infection with symptoms such as fever with severely impaired general condition or fever with local infection symptoms, like sore throat/mouth or difficulty urinating. This may be a sign that the white blood cells are affected, a condition called **agranulocytosis** (*frequency not known - cannot be estimated from available data*). Your doctor will take a blood sample to check this.

- suicidal thoughts or suicide attempts (*uncommon side effect*).

Additional side effects
Very common side effects – affect more than one in ten users:
- weight loss.
- anxiety, depression, insomnia.
- involuntary movements (dyskinesia).
- worsening of Parkinson's disease symptoms.
- dizziness when you stand up or change positions (orthostatic hypotension) – this is caused by low blood pressure.
- nausea, constipation, diarrhoea.
- pain in muscles, tissues, and skeleton.
- abnormal urine colour (chromaturia).
- risk of falling.
- urinary tract infection.

Common side effects – affect up to one in ten users:
- anaemia.
- high levels of amino acids (such as homocysteine) in the blood; vitamin B6 and B12 deficiency.
- loss of appetite, weight gain.
- nightmares, acting out, restlessness, confusion, hallucinations, psychotic disorders.
- sleep attacks, sleepiness, sleep disorders.
- dizziness, fainting, headache.
- decreased sensation of touch, sense of tingling or numbness in the skin.
- nerve disorder, with discomfort, pain and tingling, particularly in the feet (polyneuropathy).

- involuntary, persistent muscle contractions that lead to repeated twisting movement or abnormal body position (dystonia), excessive movements (hyperkinesia), shaking (tremor).
- changes in the effect on Parkinson's symptoms (On/Off episodes).
- blurred vision.
- irregular heartbeat, cardiovascular disease other than heart attack (such as angina).
- high or low blood pressure.
- breathing difficulties, pneumonia due to foreign material in the lungs.
- pain in the mouth or throat.
- abdominal distension, abdominal pain, abdominal discomfort, sensitive stomach with pain, heartburn, bloating, vomiting.
- dry mouth, changed perception of taste.
- difficulty swallowing, sore throat.
- contact dermatitis, itching, skin rash.
- severe sweating.
- pain, joint pain, neck pain, muscle spasms.
- urine leakage (urinary incontinence), difficulty urinating.
- weakness, fatigue, chest pain.
- gait disturbance.
- swelling in the legs or feet.

Impulse control disorders – changes in behaviour. This is a common side effect *(may affect up to one in ten users):*
Inability to resist the urge to perform an action that may be harmful, including:
- a strong impulse to gamble too much, despite serious effects on you or your family.
- a change or increase in sexual thoughts and behaviour of significant concern to you or to others. This could include an increased sexual drive.
- an uncontrollable and excessive need to buy things and spend money.
- binge eating (eating large amounts of food in a short time) or compulsive eating (eating more food than normal and more than what you need to satisfy your hunger).

Tell your doctor if you, your family or carer notice any of these behaviours. Your doctor will discuss ways to manage or reduce the symptoms.

Uncommon side effects – affect up to one in 100 users:
- low number of white blood cells or platelets in the blood, which may cause bleeding.
- suicide.
- confusion, elevated mood (euphoric mood), fear, nightmares.
- trouble coordinating muscle movements, convulsions.
- twitching or cramping in your eyelids that make it hard to open your eyes, double vision, optic nerve damage, narrow angle glaucoma (acute elevated pressure in the eye).
- heart palpitations, heart attack.
- inflammation in the veins.
- voice change.
- inflammation in the large intestine, bleeding in the gastrointestinal tract.
- abnormally increased production of saliva.
- abnormal liver function test results.
- skin redness, hives.
- hair loss, discolouration of nails, skin, hair or sweat.
- feeling unwell.

Rare side effects – affect up to one in 1,000 users:
- abnormal thoughts.
- abnormal breathing pattern.
- grinding of the teeth, pain in the tongue, discoloured saliva.

- hiccups.
- skin cancer (malignant melanoma) (see section 2 under 'Do not use this medicine if').
- persistent and painful erection.

Side effects of unknown frequency (side effects whose frequency has not been established yet):
- liver inflammation (hepatitis).
- abnormal laboratory results from blood and urine samples.
- memory impairment, dementia.
- Craving for large doses of Lecigon in excess of that required to control motor symptoms, known as dopamine dysregulation syndrome. Some patients experience severe abnormal involuntary movements (dyskinesia), mood swings or other side effects after taking large doses of Lecigon.

Side effects of the pump, tube, or surgery:
Very common side effects – affect more than one in ten users:
- abdominal pain.
- infection of the wound after surgery.
- thick scarring at the site of the incision.
- problems with tube insertion, such as pain or swelling in the mouth or throat, difficulty swallowing, stomach discomfort, pain or swelling, injury to the throat, mouth or stomach, internal bleeding, vomiting, bloated stomach, anxiety.
- problems at the site of the incision, redness, soreness, stoma leakage, pain or irritation.

Common side effects – affect up to one in ten users:
- abdominal discomfort, upper abdominal pain.
- infection at the surgery site or in the intestine, infection after surgery when the tube was positioned in the intestine.
- inflammation of the peritoneum (peritonitis).
- the tube changes position, for example, from the intestine to the stomach or is blocked, which can lead to decreased response to treatment.
- problems in the gastrointestinal tract due to the stoma (where the tube enters the abdomen), pain at the incision, bowel movements stop after surgery, and problems, discomfort or bleeding as a result of the treatment procedure.

Uncommon side effects – affect up to one in 100 users:
- inflammation of the large intestine or pancreas.
- inflammation of the pancreas (pancreatitis).
- the tube penetrates the large intestine wall.
- blockage in the intestines, bleeding or ulcer in the small intestine.
- part of the intestine folds into the section next to it (intussusception).
- blockage of the tube due to undigested food getting stuck around the tube.
- abscess after insertion of the tube in the intestine.

Side effects of unknown frequency (side effects whose frequency has not been established yet):
- reduced blood flow in the small intestine.
- the tube penetrates the stomach wall or small intestine.
- blood poisoning (sepsis).

Side effects when levodopa and carbidopa are taken by mouth
The following side effects have been reported with levodopa and carbidopa (the same active substances as in Lecigon) when taken by mouth. These side effects could also occur with Lecigon.

Rare side effects – affect up to one in 1,000 users:
- anaemia due to increased breakdown of red blood cells.
- inability to open the mouth all the way.
- symptoms on one side of the face, including drooping eyelids (Horner's syndrome).
- widening of the pupil in the eye, convulsive movement of the eyeballs to a fixed position, usually upwards.
- inflammation of the small blood vessels causing, among other things, raised bruises (Henoch-Schönlein purpura).

Very rare side effects – affect up to one in 10,000 users:
- changes in blood counts.

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.

You can report side effects to the Ministry of Health by following the 'Reporting Side Effects of Drug Treatment' link on the Ministry of Health home page (www.health.gov.il), which opens an online form for reporting side effects, or you can use this link: https://sideeffects.health.gov.il

5. How to store the medicine?

Prevent poisoning! To prevent poisoning, keep this and all other medicines in a closed place, out of the reach and sight of children and/or infants. Do not induce vomiting unless explicitly instructed to do so by your doctor.
Do not use the medicine after the expiry date (exp. date) which is stated on the package/label. The expiry date refers to the last day of that month.

Storage conditions
Unopened cartridge: Keep refrigerated (2°C – 8°C). Do not freeze. Store in the original packaging in order to protect from light.

Opened cartridge: Use immediately. The product can be used for up to 24 hours after being removed from the refrigerator. The pump with installed cartridge can be worn close to the body for up to 16 hours. During overnight treatment, the pump should not be worn next to the body but can, for example, be kept on the bedside table. Discard any unused amount after 24 hours.

The cartridges are intended for single use only. Do not reuse an opened cartridge.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Additional information

In addition to the active ingredients, this medicine also contains:
carmellose sodium, hydrochloric acid, sodium hydroxide, purified water.

What the medicine looks like and contents of the pack:
Opaque, viscous, yellow or yellowish-red gel.
The container is a plastic cartridge containing 47 ml of intestinal gel.

One pack contains 7 cartridges.

Registration holder's name and address:
TrueMed Ltd., 10 Beni Gaon St., Poleg Industrial Park, P.O.B. 8105, Netanya 4250499

Manufacturer's name and address:
Lobsor Pharmaceuticals, Kålsängsgränd 10 D, 753 19 Uppsala, Sweden

This leaflet was revised in November 2023 according to Ministry of Health guidelines.

Registration number of the medicine in the Ministry of Health's National Drug Registry:
173 28 37033

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