Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986

This medicine is dispensed with a doctor's prescription only

Lonsurf 15 mg / 6.14 mg
Lonsurf 20 mg / 8.19 mg
Film-coated tablets

Name and quantity of active ingredients:

Lonsurf 15 mg / 6.14 mg

Each film-coated tablet contains:
trifluridine 15 mg
tipiracil (as hydrochloride) 6.14 mg

Lonsurf 20 mg / 8.19 mg

Each film-coated tablet contains:
trifluridine 20 mg
tipiracil (as hydrochloride) 8.19 mg

Inactive ingredients and allergens in this medicine: see section 6 **'Additional information'.**
See also **'Important information about some of this medicine's ingredients'** in section 2**.**

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?

Lonsurf is intended for treating adults with metastatic colon or rectal cancer (colorectal cancer (CRC)) and stomach cancer (inluding cancer in the join between the esophagus and the stomach).

- This medicine is intended to treat cancer when it has spread to other organs in the body.
- This medicine is intended for use when other treatments have failed or when other treatments are not right for you.

Therapeutic group: anticancer, antimetabolites.

Lonsurf contains 2 different active ingredients: Trifluridine and Tipiracil.

- Trifluridine stops the growth of cancer cells.
- Tipiracil stops the trifluridine from being broken down by the body, helping trifluridine to work longer.

2. Before using this medicine

Do not use this medicine if:

- You are sensitive (allergic) to the active ingredients (Trifluridine or Tipiracil) or to any of the other ingredients in this medicine (see section 6 '**Additional Information**').

Do not take Lonsurf if the above applies to you. If you are not sure, talk to your doctor before taking Lonsurf.

Special warnings about using this medicine

Tell your doctor or pharmacist before taking Lonsurf if:

- you have kidney problems
- you have liver problems

If you are not sure, talk to your doctor or pharmacist before taking Lonsurf.

Treatment may lead to the following side effects (see section 4 '**Side effects**'):

- a reduced number of certain types of white blood cells (neutropenia) which are important for protecting the body against bacterial or fungal infections. As a consequence of neutropenia, fever (febrile neutropenia) and blood infection (septic shock) may occur.
- a reduced number of red blood cells (anemia)
- a reduced number of platelets in the blood (thrombocytopenia) which are important to stop bleeding and work by clumping and clotting blood when there are blood vessel injuries
- gastrointestinal problems.

Children and adolescents:

Lonsurf is not intended for use in children and adolescents under 18 years old.

Tests and follow-up:

Your doctor will order blood tests before each Lonsurf treatment cycle. A new treatment cycle will be started every 4 weeks. The tests are needed because Lonsurf can sometimes affect your blood cells.

Other medicines and Lonsurf:

If you are taking or have recently taken other medicines, including nonprescription medications, herbal remedies, and dietary supplements, tell your doctor or pharmacist.

This is because Lonsurf can affect the way some other medicines work.

Also some other medicines can affect the way Lonsurf works.

In particular tell your doctor or pharmacist if you are taking medicines used to treat HIV, such as zidovudine.

This is because zidovudine may not work as well if you are taking Lonsurf.

Talk to your doctor about whether to switch to a different HIV medicine.

If the above applies to you (or you are not sure), talk to your doctor or pharmacist before taking Lonsurf.

Using this medicine and food:
Take within 1 hour after your morning and evening meal.

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

Pregnancy
If you become pregnant, you and your doctor will have to decide if the benefits of Lonsurf are greater than the risk of harm to your unborn baby.

Breastfeeding
Do not breastfeed if you are taking Lonsurf as it is not known whether Lonsurf passes into breast milk.

Contraception
You must not become pregnant while taking this medicine. This is because it may harm your unborn baby. You and your partner should use effective methods of contraception while taking this medicine. You should also do this for 6 months after you stop taking the medicine. If you are a woman and you become pregnant during this time, or if you are a man and your partner becomes pregnant during this time, you must talk to your doctor or pharmacist straight away.

Driving and using machines:
Lonsurf has a slight effect on your ability to drive and use machines. Side effects like tiredness, dizziness, and nausea may occur during the course of treatment and may affect your ability to drive and operate machines. Do not drive or use any tools or machines if you experience symptoms that affect your ability to concentrate or react.

Important information about some of this medicine's ingredients:
If you have been told by your doctor that you have an intolerance to certain sugars, contact your doctor before taking this medicine.

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.
Your dose depends on your weight and height.
Your doctor will tell you how many tablets to take each time. You will take a dose 2 times a day.

You will take Lonsurf for 10 days during the first 2 weeks, and then stop the medicine for 2 weeks. This 4 week period is called a 'cycle.' The specific dosing schedule is as follows:

- **Week 1**
  - take the dose 2 times a day for 5 days
  - then stop taking the medicine for 2 days - no medicine
- **Week 2**
  - take the dose 2 times a day for 5 days
  - then stop taking the medicine for 2 days - no medicine
- **Week 3**
  - no medicine
- **Week 4**
  - no medicine

You will then start again with another cycle of 4 weeks following the schedule described above.

Lonsurf comes in two strengths. Your doctor may prescribe both strengths for your prescribed dose.
Do not exceed the recommended dose.

Taking this medicine:
- Take this medicine by mouth.
- Swallow the tablets whole with a glass of water.
- Take within 1 hour after your morning and evening meal.
- Wash your hands after handling this medicine.

If you have accidentally taken a higher dose of Lonsurf than you need
If you have taken an overdose, or if a child has accidentally swallowed some medicine, immediately see a doctor or go to a hospital emergency room and bring the medicine package with you.

If you forget to take Lonsurf at the scheduled time
- If you forget to take a dose, talk to your doctor or pharmacist.
- Do not take a double dose to make up for a forgotten dose.

Adhere to the treatment as recommended by your doctor. Even if your health improves, do not stop taking this medicine without consulting your doctor first.

Do not take medicines in the dark! Check the label and the dose <u>each time</u> you take a 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>

Like with all medicines, using Lonsurf may cause side effects in some users.
Do not be alarmed by this list of side effects; you may not experience any of them.

Serious side effects

Tell your doctor immediately if you notice any of the following serious side effects (many of the side effects are seen in laboratory tests - for example those affecting your blood cells):

- Neutropenia (*very common*), febrile neutropenia (*common*) and septic shock (*uncommon*). The signs include chills, fever, sweating or other sign of bacterial or fungal infection (see section 2).
- Anemia *(very common).* The signs include feeling short of breath, tiredness or looking pale (see section 2).
- Vomiting (*very common*) and diarrhea (*very common*), which may lead to dehydration if they are severe or persistent.
- Severe gastrointestinal problems: abdominal pain *(common)*, ascites *(uncommon)*, colitis *(uncommon)*, acute pancreatitis *(uncommon),* bowel obstruction (ileus) *(uncommon),* and partial bowel obstruction (subileus) *(uncommon)*. The signs include intense abdominal pain that can be associated with vomiting, blocked or partly blocked bowel, fever, or swelling of the abdomen.
- Thrombocytopenia (*very common*). The signs include unusual bruising or bleeding (see section 2).
- Pulmonary embolism *(uncommon)*: blood clots in lungs. The signs include shortness of breath and pain in the chest or in the legs.
- Interstitial lung disease has been reported in patients receiving the medicine. The signs include difficulty in breathing, shortness of breath, with cough or fever.

Some of these serious side effects may lead to death.

Other side effects

Tell your doctor if you notice any of the following side effects. Many of the side effects are seen in laboratory tests - for example those affecting your blood cells. Your doctor will be looking out for these side effects in your test results.

Very common side effects: may affect more than 1 in 10 people:

- decreased appetite
- feeling very tired
- nausea
- reduced white blood cells called leucocytes - can increase your risk for infection

Common side effects: may affect up to 1 in 10 people:

- fever
- hair loss
- weight loss
- changes in the way things taste
- constipation
- feeling generally unwell
- low levels of albumin or total protein in the blood
- increased bilirubin in your blood - can cause yellowing of skin or eyes
- reduced number of white blood cells called lymphocytes - can increase your risk of infection
- swelling in your hands or legs or feet
- redness, swelling, pain on the palms of your hands and soles of your feet (hand-foot syndrome)
- feeling of numbness or pins and needles in hands or feet
- mouth problems or pain

- swelling of mucous membranes - this could be inside the nose, mouth, throat, eyes, vagina, lungs or gut
- increased liver enzymes
- protein in your urine
- rash, itchy or flaky skin

Uncommon side effects: may affect up to 1 in 100 people:
- low or high blood pressure
- blood clots, for example in the brain or legs
- blood test results indicating problems with clotting that make you bleed more easily
- more noticeable heart-beat, chest pain
- abnormal increase or decrease in heart rate
- changes in your heart trace (ECG - electrocardiogram)
- increased number of white blood cells
- increased number of white blood cells called monocytes
- increased lactate dehydrogenase level in your blood
- low levels of phosphates, sodium, potassium or calcium in your blood
- reduced number of white blood cells called granulocytes or monocytes - can increase your risk of infection
- high blood sugar (hyperglycemia), increased salt, urea, creatinine and potassium in your blood
- blood test result indicating inflammation (increased C-reactive protein)
- ear pain
- feeling of spinning (vertigo)
- feeling dizzy, headache
- runny or bloody nose, sinus problems
- sore throat, hoarse voice, problems with your voice
- redness, itching of the eye, eye infections, watery eyes
- dry eyes
- vision problems such as blurred vision, double vision, decreased vision, cataracts
- dehydration
- bloating, passing gas, indigestion
- pain or inflammation in upper or lower part of digestive tract
- inflammation, swelling or bleeding in your bowel
- inflammation and infection in your gut
- inflammation or increased acid in your stomach or gullet, reflux
- painful tongue, polyps inside your mouth, mouth ulcers, retching
- bad breath, tooth decay, tooth or gum problems, bleeding gums, gum infections
- dry skin
- skin flushing
- swelling or pain in your joints or big toes
- pain or discomfort in your arms or legs
- pain, including pain from the cancer
- bone pain, muscle pain, muscle weakness or spasms, pain in tendons, nerves or ligaments
- feeling of being cold

- shingles (pain and vesicular rash on skin over nerve tracts affected by nerve inflammation from herpes zoster virus)
- liver disorder
- inflammation or infection of bile ducts, increase in the diameter of the bile duct
- kidney failure
- viral infections
- cough, feeling short of breath, infection of the sinuses, throat, airway or lungs, chest infections
- inflammation or infection in your bladder
- changes in urine test, blood in urine
- problems passing urine (urine retention), loss of bladder control (incontinence)
- fungal infection of feet (athlete's foot), candida infections (candidiasis)
- accumulation of fluid in the lungs
- changes in the menstrual cycle
- anxiety
- passing out (syncope)
- burning sensation, unpleasant, increased or loss of sense of touch and other non-severe neurological problems
- raised itchy rash, red skin, blisters, skin sloughing off, hives, acne
- increased sweating, sensitivity to light, nail problems
- problem with sleeping or falling asleep

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.

Reporting side effects
You can report side effects to the Ministry of Health by following the link 'Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. You can also 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 a doctor.

Do not use the medicine after the expiry date (exp. date) which is stated on the package or blister tray. The expiry date refers to the last day of that month.

Storage conditions:
Store below 30°C.

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:
Lonsurf 15 mg/6.14 mg:
Tablet core:
lactose monohydrate, starch pregelatinised (maize), stearic acid.
Coating:
hypromellose (substitution type 2910), macrogol (8000), titanium dioxide (E171), magnesium stearate.
Printing ink:
shellac, iron oxide red (E172), iron oxide yellow (E172), titanium dioxide (E171),
indigo carmine aluminium lake (E132), carnauba wax, talc.

Lonsurf 20 mg/8.19 mg:
Tablet core:
lactose monohydrate, starch pregelatinised (maize), stearic acid.
Coating:
hypromellose (substitution type 2910), macrogol (8000), titanium dioxide (E171), iron oxide red (E172), magnesium stearate.
Printing ink:
shellac, iron oxide red (E172), iron oxide yellow (E172), titanium dioxide (E171),
indigo carmine aluminium lake (E132), carnauba wax, talc.

What the medicine looks like and contents of the pack:
Lonsurf 15 mg/6.14 mg:
white, biconvex, round, film-coated tablets, printed with “15” on one side and “102” and “15 mg” on the other side in grey ink.

Lonsurf 20 mg/8.19 mg:
pale red, biconvex, round, film-coated tablet, printed with “20” on one side and “102” and “20 mg” on the other side in grey ink.

Each pack contains 20 film-coated tablets (2 blisters of 10 tablets each) or 40 film-coated tablets (4 blisters of 10 tablets each), or 60 film-coated tablets (6 blisters of 10 tablets each).

Not all pack sizes may be marketed.

Registration holder’s name and address:
Medison Pharma Ltd., 10 Hashiloach st., POB 7090, Petach Tikva.

Manufacturer’s name and address:
Les Laboratoires Servier, 50 rue Carnot, 92284 Suresnes Cedex, France.

This leaflet was revised in January 2021.

Registration number of the medicine in the Ministry of Health’s National Drug Registry:
Lonsurf 15 mg / 6.14 mg: 163-89-35314
Lonsurf 20 mg / 8.19 mg: 163-90-35315