PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986

The medicine is dispensed with a doctor's prescription only

TAFINLAR® 50 mg

Each hard capsule contains:
Dabrafenib (as mesilate) 50 mg

TAFINLAR® 75 mg

Each hard capsule contains:
Dabrafenib (as mesilate) 75 mg

For the list of inactive and allergenic ingredients in the preparation see section 6 "Further information".

Read this leaflet carefully in its entirety before using the medicine. This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.

This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar.

1. WHAT IS THE MEDICINE INTENDED FOR?

Tafinlar is a medicine that contains the active substance dabrafenib. It is used either on its own or in combination with another medicine containing trametinib, to treat adults with a type of skin cancer called melanoma that has spread to other parts of the body or cannot be surgically resected, with a mutation in the BRAF gene (BRAF V600 mutation).

Tafinlar in combination with trametinib is also used as a complementary treatment in adults with stage 3 melanoma with the BRAF gene mutation (BRAF V600 mutation) after the lesion has been fully removed by surgery.

Tafinlar in combination with trametinib is also used to treat adults who have advanced-stage lung cancer called non-small cell lung cancer (NSCLC), with the BRAF gene mutation (BRAF V600 mutation).

Tafinlar in combination with trametinib is indicated to treat a type of thyroid cancer called anaplastic thyroid cancer (ATC) with a mutation in the BRAF gene (BRAF V600E mutation), and which has spread to other parts of the body or locally advanced and with no satisfactory results from local treatment.

Tafinlar in combination with trametinib is indicated to treat solid tumors in adults and children aged 6 and above that cannot be removed with surgery or have spread to other parts of the body, and that have gotten worse (progressed) and for which there are no other satisfactory treatment options with a BRAF gene mutation (BRAF V600E mutation). Tafinlar is not intended to treat colon and rectal cancer.

Tafinlar in combination with trametinib is indicated for the treatment of a type of brain cancer called low-grade glioma (LGG) in children 6 years of age and older with a BRAF gene mutation (BRAF V600E mutation) and who require systemic therapy.

Therapeutic group: protein kinase inhibitor.

In all of these cancer types there is a particular change (mutation) in the gene called BRAF at the V600 position.

The mutation in this gene may have caused the cancer to develop. Your medicine targets proteins made from this modified gene and slows down or stops the development of your cancer.

2. BEFORE USING THE MEDICINE

Tafinlar should only be used to treat melanomas, non-small cell lung cancer (NSCLC), anaplastic thyroid cancer (ATC), in solid tumors and low-grade glioma with a mutation in the BRAF gene. Therefore, before starting treatment your doctor will test for this mutation.

If your doctor decides that you will receive treatment with the combination of Tafinlar and trametinib, **read the trametinib leaflet carefully as well as this leaflet.**

If you have any further questions regarding use of this medicine, refer to the doctor or pharmacist.

Do not use the medicine if:

you are sensitive (allergic) to dabrafenib, or any of the additional ingredients contained in the medicine (listed in section 6).
Check with your doctor if you think this applies to you.

Special warnings regarding use of the medicine

Before the treatment with Tafinlar, tell the doctor if you:

- have any **liver problems**.
- have or have ever had any **kidney problems**.
  Your doctor may take blood samples to monitor your liver and kidney function while you are taking Tafinlar.
- **have had a different type of cancer other than melanoma, non-small cell lung cancer (NSCLC), anaplastic thyroid cancer (ATC) or solid tumors,** as you may be at greater risk of developing other skin and non-skin cancers when taking Tafinlar.

Before you take Tafinlar in combination with trametinib, your doctor needs to know if:

- you have heart problems such as heart failure or problems with the way your heart beats.
- you have eye problems including blockage of the vein draining the eye (retinal vein occlusion) or swelling in the eye which may be caused by fluid leakage (chorioretinopathy).
- you have any lung or breathing problems, including difficulty in breathing occasionally accompanied by a dry cough, shortness of breath and fatigue.
- you have or have had problems in the digestive system, such as diverticulitis (inflamed pouches in the large intestine) or metastases in the digestive system.

Check with your doctor if you think any of these apply to you.

Conditions you need to look out for

Some people taking Tafinlar develop other conditions, which can be serious. You need to know about important signs and symptoms to look out for while you are taking this medicine. Some of these symptoms (bleeding, fever, changes in your skin and eye problems) are briefly mentioned in this section, but more detailed information is found in section 4, "Side effects".

Bleeding

Taking Tafinlar in combination with trametinib can cause serious bleeding, including in your brain, the digestive system (such as stomach, rectum or intestine), lungs, and other organs, and can lead to death. Symptoms may include:

- headaches, dizziness, or feeling weak
- blood in the stools or black stools
- blood in the urine
- stomach pain
- coughing/vomiting up blood

Tell your doctor as soon as possible if you get any of these symptoms.

Fever

Taking Tafinlar or the combination of Tafinlar and trametinib may cause fever, although it is more likely if you are taking the combination treatment (see also section 4). In some cases, people with fever may develop low blood pressure, dizziness or other symptoms. **Tell your doctor immediately if you get a temperature** above 38°C or if you feel a fever coming on while you are taking this medicine.

Heart problems

- Tafinlar can cause heart problems, or make existing heart problems worse (see also "Heart conditions" in section 4), in people taking Tafinlar in combination with trametinib.
- **Tell your doctor if you have a heart problem.** Your doctor will run tests to check that your heart is working properly before and during your treatment with Tafinlar in combination with trametinib. Tell your doctor immediately if it feels as if your heart is pounding, racing, or beating irregularly, or if you experience dizziness, tiredness, lightheadedness, shortness of breath or swelling of the legs. If necessary, your doctor may decide to interrupt your treatment temporarily or to stop it altogether.

Changes in your skin which may indicate new skin cancer

Your doctor will check your skin before you start taking this medicine and regularly while you are taking it.

Tell your doctor immediately if you notice any changes in your skin while taking this medicine or after treatment (see also section 4).

Eye problems

You should undergo an eye examination by your doctor while you are taking this medicine.

Tell your doctor immediately if you get eye redness and irritation, blurred vision, eye pain or other vision changes during your treatment (see also section 4).

Tafinlar when given in combination with trametinib, can cause eye problems including blindness. Trametinib is not recommended if you have ever had blockage of the vein draining the eye (retinal vein occlusion). Tell your doctor immediately if you get the following symptoms of eye problems: blurred vision, loss of vision or other vision changes, colored dots in your vision or halos (seeing blurred outlines around objects) during your treatment. If necessary, your doctor may decide to interrupt your treatment temporarily or to stop it altogether.

⟶**Read the information about fever, changes in your skin and eye problems in section 4 of this leaflet. Tell your doctor or pharmacist if you get any of the signs and symptoms listed.**

Liver problems

Tafinlar in combination with trametinib, can cause problems with your liver which may develop into serious conditions such as hepatitis and liver failure, which may be fatal. Your doctor will monitor you periodically. Signs that your liver may not be working properly may include:

- Loss of appetite
- Nausea
- Vomiting
- Stomach pain
- Yellowing of the skin or the whites of your eyes (jaundice)
- Dark-colored urine
- Itching of your skin

Tell your doctor as soon as possible if you get any of these symptoms.

Muscle pain

Tafinlar in combination with trametinib, can result in the breakdown of muscle tissue (rhabdomyolysis). **Tell your doctor** as soon as possible if you get any of these symptoms:

- muscle pain
- dark urine due to kidney damage

If necessary, your doctor may decide to interrupt your treatment temporarily or to stop it altogether.

Hole in the stomach or intestine (perforation)

Taking a combination of Tafinlar with trametinib may increase the risk of development of perforations in the wall of the intestine.

Tell the doctor as soon as possible if you experience severe abdominal pain.

Serious skin reactions

Serious skin reactions have been reported in people taking Tafinlar in combination with trametinib. Tell the doctor immediately if you notice any changes in your skin (see section 4 for symptoms to be aware of).

Inflammatory disease mainly affecting the skin, lung, eyes and lymph nodes

An inflammatory disease mainly affecting the skin, lung, eyes and lymph nodes (sarcoidosis). Common symptoms of sarcoidosis may include coughing, shortness of breath, swollen lymph nodes, visual disturbances, fever, fatigue, pain and swelling in the joints and tender bumps on your skin.

Tell your doctor if you get any of these symptoms.

Immune system disorders

Tafinlar in combination with trametinib may in rare instances cause a condition (haemophagocytic lymphohistiocytosis, or HLH) in which the immune system makes too many infection fighting cells, called histiocytes and lymphocytes. Symptoms may include enlarged liver and/or spleen, skin rash, lymph node enlargement, breathing problems, easy bruising, kidney abnormalities, and heart problems.

Tell your doctor immediately if you experience multiple symptoms such as fever, swollen lymph glands, bruising or skin rash, at the same time.

Tumor lysis syndrome

If you experience the following symptoms, tell your doctor immediately as this can be a life-threatening condition: nausea, shortness of breath, irregular heartbeat, muscular cramps, seizures, clouding of urine, decrease in urine output and tiredness. These symptoms may be caused by a group of metabolic complications that can occur during treatment of cancer that are caused by the breakdown products of dying cancer cells (tumor lysis syndrome or TLS) and can lead to changes in kidney function (see also section 4).

Children and adolescents

Tafinlar is not intended for children under the age of 6 years. The safety and efficacy of Tafinlar in combination with trametinib in children under the age of 6 years are unknown.

The safety and efficacy of Tafinlar monotherapy in children are unknown.

Drug interactions

Before starting treatment, tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including non-prescription medicines and nutritional supplements.

Some medicines may affect how Tafinlar works, or increase the risk of side effects. Tafinlar can also affect how other medicines work. These include:

- **birth control medicines** (contraceptives) containing hormones, such as pills, injections, or patches
- warfarin and acenocoumarol, medicines used to **thin the blood**
- digoxin, used to treat **heart problems**
- medicines to treat **fungal infections**, such as ketoconazole, itraconazole, voriconazole and posaconazole
- some calcium channel blockers, used to treat **high blood pressure**, such as diltiazem, felodipine, nicardipine, nifedipine or verapamil
- medicines to treat **cancer,** such as cabazitaxel
- some medicines to **lower fat (lipids)** in the bloodstream, such as gemfibrozil
- some medicines used to treat certain **psychiatric problems**, such as haloperidol
- some **antibiotics**, such as clarithromycin, doxycycline and telithromycin
- some medicines for treating **tuberculosis** (TB), such as rifampicin
- some medicines that reduce **cholesterol** levels, such as atorvastatin and simvastatin
- some **immunosuppressants**, such as cyclosporin, tacrolimus and sirolimus
- some **anti-inflammatory** medicines, such as dexamethasone and methylprednisolone
- some medicines to treat **HIV** (human immunodeficiency virus), such as ritonavir, amprenavir, indinavir, darunavir, delavirdine, efavirenz, fosamprenavir, lopinavir, nelfinavir, tipranavir, saquinavir and atazanavir
- some medicines used for **pain relief**, such as fentanyl and methadone
- medicines to treat seizures (**epilepsy**), such as phenytoin, phenobarbital, primidone, valproic acid or carbamazepine
- **antidepressants** such as nefazodone and the herbal medicine St. John's wort (Hypericum)
- some **sedatives (hypnotics)** medicines such as diazepam, midazolam, zolpidem

Tell your doctor or pharmacist if you are taking any of these medicines (or if you are not sure). Your doctor may decide to adjust your dosage.

Keep a list of the medicines you take, so you can show it to your doctor or pharmacist.

Use of the medicine and food

Take Tafinlar on an empty stomach. This means that:

- after taking Tafinlar, you must wait **at least 1 hour** before eating, or
- after eating, you must wait **at least 2 hours** before taking Tafinlar

Pregnancy, breast-feeding and fertility

Tafinlar is not recommended during pregnancy.

- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. Tafinlar is not recommended during pregnancy, since it may potentially harm an unborn baby.
- If you are a woman who could become pregnant, you must use a reliable birth control method while you are taking Tafinlar and for at least 2 weeks after you stop taking it and for at least 16 weeks following the last dose of trametinib, when given in combination with Tafinlar.
- Birth control medicines containing hormones (such as pills, injections or patches) may not work as effectively while you are taking Tafinlar or combination treatment (Tafinlar as well as trametinib). You need to use another effective method of birth control, so you do not become pregnant while you are taking this medicine. Ask your doctor or pharmacist for advice.
- If you do become pregnant while you are taking this medicine, tell your doctor immediately.

Tafinlar is not recommended while breast-feeding.

It is not known whether the ingredients of this medicine can pass into breast milk.

If you are breast-feeding, or planning to breast-feed, you must tell your doctor. You and your doctor will decide whether you will take this medicine or breast-feed.

Fertility – both men and women

Animal studies have shown that the active substance dabrafenib may permanently reduce male fertility. In addition, men who are taking Tafinlar may have a reduced sperm count and their sperm count may not return to normal levels after they stop taking this medicine.

Prior to starting treatment with Tafinlar, talk to your doctor about options to improve your chances to have children in the future.

Taking Tafinlar with trametinib: trametinib may impair fertility in both men and women.

If you have any further questions on the effect of this medicine on sperm count, ask your doctor or pharmacist.

Driving and using machines

Tafinlar can have side effects that may affect your ability to drive or use machines.

Avoid driving or using machines if you have problems with your vision or if you feel tired or weak, or if your energy levels are low.

Descriptions of these effects can be found in sections 2 and 4.

Discuss with your doctor or pharmacist if you are unsure about anything. Even your disease, symptoms and treatment situation may affect your ability to drive or use machines.

3. HOW SHOULD YOU USE THE MEDICINE?

Always use the preparation according to the doctor's instructions. Check with the doctor or pharmacist if you are uncertain about the dosage and treatment regimen of the preparation.

The dosage and treatment regimen will be determined by the doctor only.

The usual dosage of Tafinlar either used alone or in combination with trametinib in adults, is generally two 75 mg capsules twice a day (corresponding to a daily dose of 300 mg). The usual dosage of trametinib, when taken in combination with Tafinlar, is 2 mg once a day.

The dosage and treatment regimen for children and adolescents will be determined by the doctor only.

Your doctor may decide that you should take a lower dose if you develop side effects.

Tafinlar is also available as 50 mg capsules if a dose reduction is recommended.

Do not exceed the recommended dose, since this may increase the risk of side effects.

Method of administration

Swallow the capsules whole with water, one after the other.

Do not chew or crush the capsules, since they will lose their effect.

Take Tafinlar twice a day, on an empty stomach. This means that:

- after taking Tafinlar, you must wait **at least 1 hour** before eating.
- after eating, you must wait **at least 2 hours** before taking Tafinlar.

Take Tafinlar in the morning and evening, about 12 hours apart. Take your morning and evening doses of Tafinlar at the same times every day. This will increase the chance of remembering to take the capsules.

Do not take the morning and evening doses of Tafinlar at the same time.

In case of vomiting after taking the medicine, do not take another dose. Take your next dose at the usual time.

If you accidentally took a higher dosage

If you took an overdose or if a child has accidentally swallowed the medicine, refer immediately to a doctor or proceed to a hospital emergency room, and bring the package of the medicine with you.

If you forget to take the medicine

If the missed dose is less than 6 hours late, take it as soon as you remember.

If the missed dose is more than 6 hours late, skip that dose and take your next dose at the usual time. Then carry on taking your capsules at the regular times, as usual.

Do not take a double dose to make up for a missed dose.

If you stop taking the medicine

Adhere to the treatment regimen as recommended by the doctor. Do not stop unless your doctor or pharmacist advises you to.

Do not take medicines in the dark! Check the label and the dose
each time you take medicine. Wear glasses if you need them.

If you have further questions regarding use of the medicine, consult a doctor or pharmacist.

How should you take Tafinlar in combination with trametinib

- Take Tafinlar in combination with trametinib exactly as your doctor tells you. Do not change your dose and do not stop taking Tafinlar or trametinib unless your doctor tells you.
- Take **Tafinlar twice daily** and take **trametinib once daily**. It may be better for you to adopt the habit of taking both medicines at the same time each day. The Tafinlar doses should be about 12 hours apart. Trametinib, when given in combination with Tafinlar, should preferably be taken with **either** the morning dose of Tafinlar **or** the evening dose of Tafinlar.
- Take Tafinlar and trametinib on an empty stomach, at least one hour before or two hours after a meal. Take them whole with a full glass of water.
- If you miss a dose of Tafinlar or trametinib, take it as soon as you remember. Do not make up for forgotten doses and just take your next dose at your regular time:
  - if there are less than 6 hours until your next scheduled dose of Tafinlar, which is taken twice daily.
  - if there are less than 12 hours until your next scheduled dose of trametinib, which is taken once daily.
- If you get side effects, your doctor may decide that you should take a lower dosage of Tafinlar and/or trametinib. Take the doses of Tafinlar and trametinib exactly as your doctor tells you.

If you have further questions regarding use of the medicine, consult the doctor or pharmacist.

4. SIDE EFFECTS

As with any medicine, use of Tafinlar may cause side effects in some users. Do not be alarmed by the list of side effects. You may not suffer from any of them.

Possible serious side effects

Bleeding problems

Tafinlar can cause serious bleeding problems, especially in your brain, when taken in combination with trametinib. Call your doctor immediately and get medical help right away if you have any unusual signs of bleeding, including:

- headache, dizziness, or weakness
- coughing up blood or blood clots
- vomit containing blood or that looks like “coffee grounds”
- red or black stools that look like tar

Fever

Taking Tafinlar may cause fever in more than one in 10 users. **Tell your doctor immediately if you develop a fever (temperature of 38°C or above) or if you feel a fever coming on while you are taking this medicine.** The doctor will perform tests to find out if there are other causes for the fever and will treat the problem.

In some cases, people with fever may develop low blood pressure and dizziness. If the fever is severe, your doctor may recommend that you stop taking Tafinlar, or Tafinlar and trametinib, while treating the fever with other medicines. Once the fever is controlled, your doctor may recommend that you start taking Tafinlar again.

Heart conditions

Tafinlar can affect the way your heart pumps blood, when taken in combination with trametinib. It is more likely to affect people who have an existing heart problem. You will be checked for any heart problems while you are taking Tafinlar in combination with trametinib. Signs and symptoms of heart problems include:

- feeling like your heart is pounding, racing, or beating irregularly
- dizziness
- tiredness
- feeling lightheaded
- shortness of breath
- swelling of the legs

Tell your doctor as soon as possible if you get any of these symptoms, either for the first time or if they get worse.

Changes in your skin

Serious skin reactions have been reported in people taking Tafinlar in combination with trametinib (frequency unknown). If you notice any of the following:

- Reddish patches on the skin that are circular or target-shaped, with central blisters. Skin peeling. Ulcers in the mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome).
- Widespread rash, fever, and enlarged lymph nodes (DRESS-syndrome or drug hypersensitivity syndrome).

→ **Stop using the medicine and seek medical attention immediately.**

Patients taking Tafinlar may commonly (1-10 in 100 users) develop a different type of skin cancer called cutaneous squamous cell carcinoma (cuSCC). Others may develop a type of skin cancer called basal cell carcinoma (BCC). Usually, these skin changes remain local and can be removed with surgery and treatment with Tafinlar can be continued without interruption.

Some people taking Tafinlar may also notice that new melanomas have appeared. These melanomas are usually removed by surgery and treatment with Tafinlar can be continued without interruption.

Your doctor will check your skin before you start taking Tafinlar, and will then check it again every month while you are taking this medicine and for 6 months after you stop taking it. This is to look for any new skin cancers.

Your doctor will also check your head, your neck, your mouth, your lymph glands and you will undergo scans of your chest and stomach area (called CT scans) regularly. You may undergo blood tests. These checks are to detect if any other cancer, including squamous cell carcinoma, develops inside your body. Pelvic examinations (for women) and anal examinations are also recommended before and at the end of your treatment.

Check your skin regularly whilst taking Tafinlar

If you notice any of the following:

- new wart
- skin sore or reddish bump that bleeds or does not heal
- change of a mole in size or color

Tell your doctor as soon as possible if you get any of these symptoms -
either for the first time or if they get worse.

Skin reactions (rash) can happen while taking Tafinlar in combination with trametinib. **Talk to your doctor** if you notice a skin rash while taking Tafinlar in combination with trametinib.

Eye problems

Patients taking Tafinlar alone can uncommonly (1-10 in 1,000 users) develop an eye problem called uveitis, which could damage your vision if it is not treated. This condition may occur commonly (1-10 in 100 users) in patients taking Tafinlar in combination with trametinib.

Uveitis may develop rapidly and the symptoms include:

- eye redness and irritation
- blurred vision
- eye pain
- increased sensitivity to light
- floating spots before the eyes

Contact your doctor immediately if you develop these symptoms.

Tafinlar can cause eye problems when taken in combination with trametinib. Trametinib is not recommended if you have ever had a blockage of the vein draining the eye (retinal vein occlusion). Your doctor may advise an eye examination before you take Tafinlar in combination with trametinib and while you are taking them. Your doctor may ask you to stop taking trametinib or refer you to a specialist, if you develop signs and symptoms in your vision that include:

- loss of vision
- eye redness or irritation
- colored dots in your vision
- halo (seeing blurred outlines around objects)
- blurred vision

Contact your doctor or pharmacist immediately if you get these symptoms.

It is very important to tell your doctor immediately if you develop these symptoms, especially if you have a painful, red eye that does not clear up quickly. He may refer you to a specialist eye doctor for a complete eye examination.

Immune system disorders

If you experience multiple symptoms such as fever, swollen lymph glands, bruising or skin rash, at the same time, tell your doctor immediately. These may be signs of a condition where the immune system makes too many infection-fighting cells called histiocytes and lymphocytes that may cause various symptoms (haemophagocytic lymphohistiocytosis), see section 2 (frequency rare).

Tumor lysis syndrome

Tell your doctor immediately if you experience the following symptoms: nausea, shortness of breath, irregular heartbeat, muscular cramps, seizures, clouding of urine,

decrease in urine output and tiredness. These symptoms may be signs of a condition resulting from a rapid breakdown of cancer cells which in some people may be fatal (tumor lysis syndrome or TLS), see section 2 (frequency unknown).

Possible side effects in patients taking Tafinlar alone

The side effects that you may see when you take Tafinlar alone are as follows:

Very common side effects (may occur in more than one in 10 users):
- Papilloma (a type of skin tumor which is usually not harmful)
- Decreased appetite
- Headache
- Cough
- Nausea, vomiting
- Diarrhea
- Thickening of the outer layers of the skin
- Unusual hair loss or thinning
- Rash
- Reddening and swelling of the palms, fingers and soles of the feet (see “Changes in your skin” earlier in section 4)
- Joint pain, muscle pain, or pain in the hands or feet
- Fever (see “Fever” earlier in section 4)
- Sense of fatigue, lack of energy
- Chills
- Feeling weak

Common side effects (may occur in 1-10 in 100 users):
- Skin effects including cutaneous squamous cell carcinoma (a type of skin cancer), wart-like growths, skin tags, uncontrolled skin growths or lesions (basal cell carcinoma), dry skin, itching or redness of the skin, patches of thick, scaly, or crusty skin (actinic keratosis), skin lesions, skin redness, increased sensitivity of the skin to sun
- Constipation
- A flu-like illness
- Nerve damage that may cause pain, loss of sensation or tingling in the hands and feet and/or muscle weakness (peripheral neuropathy)

Common side effects that may show up in your blood tests
- Low levels of phosphate (hypophosphatemia) in the blood
- Increase in blood sugar level (hyperglycemia)

Uncommon side effects (may occur in 1-10 in 1,000 users):
- New melanoma
- Allergic reaction (hypersensitivity)
- Inflammation of the eye (uveitis, see “Eye problems” earlier in section 4)
- Inflammation of the pancreas (causing strong abdominal pain)
- Inflammation of the fatty layer under the skin (panniculitis)
- Kidney problems, kidney failure
- Inflammation of kidneys
- Raised, painful, red to dark reddish-purple skin patches or sores that appear mainly on the arms, legs, face and neck, with a fever (signs of acute febrile neutrophilic dermatosis)

Possible side effects when Tafinlar and trametinib are taken together

When you take Tafinlar and trametinib together, you may get any of the side effects given in the lists above, although their frequency may change (increase or decrease).

You may also get **additional side effects due to taking trametinib** at the same time as Tafinlar.

Tell your doctor as soon as possible if you get any of these symptoms, either for the first time or if they get worse.

Please also read the trametinib package leaflet for details of the side effects you may get with trametinib.

The other side effects that you may see when you take Tafinlar in combination with trametinib are as follows:

Very common side effects (may occur in more than one in 10 users):
- Nasal and throat inflammation
- Decreased appetite
- Headache
- Dizziness
- High blood pressure (hypertension)
- Bleeding, at various sites in the body, which may be mild or serious (hemorrhage)
- Cough
- Stomach ache
- Constipation
- Diarrhea
- Nausea, vomiting
- Rash, dry skin, itching, skin reddening
- Joint pain, muscle pain, or pain in the hands or feet
- Muscle spasms
- Tiredness, lack of energy, weakness
- Chills
- Swelling of the hands or feet (peripheral edema)
- Fever
- A flu-like illness

Very common side effects that may show up in your blood tests:
- Abnormal blood test results related to the liver

Common side effects (may occur in 1-10 in 100 users):
- Infection of the urinary system
- Skin effects including infection of the skin (cellulitis), inflammation of hair follicles in the skin, nail disorders, such as nail bed changes, nail pain, infection and swelling of the cuticles, skin rash with pus-filled blisters, cutaneous squamous cell carcinoma (a type of skin cancer), papilloma (a type of skin tumor which is usually not harmful), wart-like growths, increased sensitivity of the skin to sun (see also “Changes in your skin” earlier in section 4)
- Dehydration (low levels of water or fluid)
- Blurred vision, eyesight problems, inflammation of the eye (uveitis)
- Heart pumping less efficiently
- Low blood pressure (hypotension)
- Localized tissue swelling
- Shortness of breath
- Dry mouth
- Sore mouth or mouth ulcers, inflammation of mucous membranes
- Acne-like problems
- Thickening of the outer layer of the skin (hyperkeratosis), patches of thick, scaly or crusty skin (actinic keratosis), chapping or cracking of the skin
- Increased sweating, night sweats
- Unusual hair loss or thinning
- Red, painful hands and feet
- Inflammation of the fatty layer under the skin (panniculitis)
- Inflammation of the mucosa
- Swelling of the face
- Nerve damage that may cause pain, loss of sensation or tingling in the hands and feet and/or muscle weakness (peripheral neuropathy)
- Irregular heartbeat (atrioventricular block)

Common side effects that may show up in your blood tests:
- Low levels of white blood cells
- Decrease in number of red blood cells (anemia), blood platelets (cells that help blood to clot), and in a type of white blood cells (leukopenia)
- Low levels of sodium (hyponatremia) or phosphate (hypophosphatemia) in the blood
- Increase in blood sugar level
- Increase in creatine phosphokinase, an enzyme found mainly in heart, brain, and skeletal muscle
- Increase in some substances (enzymes) produced by the liver

Uncommon side effects (may occur in 1-10 in 1,000 users):
- Appearance of new skin cancer (melanoma)
- Skin tags
- Allergic reactions (hypersensitivity)
- Eye changes including swelling in the eye caused by fluid leakage (chorioretinopathy), separation of the light-sensitive membrane at the back of the eye (the retina)

from its supporting layers (retinal detachment) and swelling around the eyes
- Heart rate that is lower than the normal range and/or a decrease in heart rate
- Inflammation of the lung (pneumonitis)
- Inflammation of the pancreas
- Inflammation in the intestine (colitis)
- Kidney failure
- Inflammation of the kidneys
- Inflammatory disease mainly affecting the skin, lung, eyes and lymph nodes (sarcoidosis)
- Raised, painful, red to dark reddish-purple skin patches or sores that appear mainly on the arms, legs, face and neck, with a fever (signs of acute febrile neutrophilic dermatosis)

Rare side effects (may occur in 1-10 in 10,000 users):
- A hole (perforation) in the stomach or intestines

Side effects of unknown frequency (effects whose frequency has not yet been determined):
- inflammation of the heart muscle (myocarditis), which may cause shortness of breath, fever, palpitations and chest pain
- inflamed, flaky skin (exfoliative dermatitis)
- Skin reactions localised in tattoos

Very common side effects in children when Tafinlar and trametinib are taken together:
- fever
- rash
- vomiting
- tiredness
- dry skin
- cough
- diarrhea
- acne
- headache
- abdominal pain
- nausea
- bleeding
- constipation
- skin inflammation around the fingernails and toenails
- muscle and bone pain
- dizziness
- upper respiratory tract infection
- increase in weight
- mouth ulcers
- sore throat

Additional side effects in children when Tafinlar and trametinib are taken together:
- peripheral neuropathy
- hair loss
- jaw pain
- reduced appetite
- anxiety
- irregular heartbeat (atrioventricular block)

Abnormalities that can show up in blood tests in children taking mekinist and dabrafenib together:
Chemistry:
- high blood sugar level
- low albumin level
- low calcium level
- reduced phosphate level
- reduced magnesium level
- increased magnesium level
- high sodium level
- reduced sodium level
- low potassium level
- high potassium level

Liver:
- increased aspartate aminotransferase
- increased alanine aminotransferase
- increased alkaline phosphatase
- increased bilirubin

Hematology:
- reduced hemoglobin level
- anemia
- reduced blood platelets level
- reduced white blood cell level
- increased white blood cell level (lymphocytes)

If a side effect occurs, if one of the side effects worsens or if you suffer from a side effect not mentioned in this leaflet, consult with the doctor or pharmacist.

Reporting side effects

Side effects can be reported to the Ministry of Health by clicking on the link “Report Side Effects of Drug Treatment” found on the Ministry of Health homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering the link:
https://sideeffects.health.gov.il
Side effects can also be reported to Novartis company via the email address: safetydesk.israel@novartis.com

5. HOW SHOULD THE MEDICINE BE STORED?

- Avoid poisoning! This medicine, and any other medicine, should be kept in a safe place out of the reach and sight of children and/or infants in order to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not use this medicine after the expiry date (exp. date) that appears on the package. The expiry date refers to the last day of that month.
- Do not store above 30°C.

6. FURTHER INFORMATION

- In addition to the active ingredient, the medicine also contains -
  Microcrystalline cellulose, magnesium stearate, colloidal silicone dioxide, red iron oxide (E172), titanium dioxide (E171), hypromellose (E464).
  Furthermore, the capsules are printed with black ink that contains:
  Shellac (E904), black iron oxide (E172), butyl alcohol, isopropyl alcohol, propylene glycol (E1520), ammonium hydroxide (E527).
- What the medicine looks like and the contents of the package –
  Tafinlar 50 mg capsules are opaque, dark red and imprinted with “GS TEW” and “50 mg”.
  Tafinlar 75 mg capsules are opaque, dark pink and imprinted with “GS LHF” and “75 mg”.
  The bottles are white and contain 28 capsules.
  The bottles also include a desiccant in a small cylinder shaped container. The desiccant must be kept inside the bottle and must not be swallowed.
- **Registration Holder and Importer and its address:** Novartis Israel Ltd., P.O.B. 9240, Tel Aviv.
- Revised in December 2025.
- Registration number of the medicine in the National Drug Registry of the Ministry of Health:
  Tafinlar 50 mg: 151 42 33976
  Tafinlar 75 mg: 151 43 33977