The medicine is dispensed with a doctor's prescription only

TAFINLAR® 50 mg

Each capsule contains: Dabrafenib (as mesilate) 50 mg

TAFINLAR® 75 ma

Each capsule contains: Dabrafenib (as mesilate) 75 mg

The list of additional ingredients is detailed in section

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.

Tafinlar is not intended for children and adolescents under 18 years of age.

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

- that has a particular change (mutation) in a gene called "BRAF",
- that has also spread to other parts of the body or cannot be removed by surgery

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

Therapeutic group: protein kinase inhibitor.

2. BEFORE USING THE MEDICINE

Tafinlar can only be used to treat melanomas with a change (mutation) in the BRAF gene, so your doctor must first take tumor tissue samples from you to test whether Tafinlar is suitable for you. 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 ☑ Do not use the medicine if:

you are sensitive (allergic) to the active

ingredient, or any of the other ingredients of the medicine (listed in section 6). Check with your doctor if you think this applies

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, as you may be at greater risk of developing non-skin cancers when taking

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.

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

 Conditions you may 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're 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
- ing up blood coughing/yomi

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

This medicine may cause fever (see also section 4). In some cases, people with fever may develop low blood pressure, dizziness or other symptoms. **Tell** your doctor or pharmacist immediately if you get a fever while you are taking this medicine.

Heart problems Tafinlar can cause heart problems, or make existing heart problems worse, 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: like your heart is pounding, racing, or beating irregularly, or if you experience dizziness, tiredness, shortness of breath or swelling of the legs. If necessary, your doctor may decide to interrupt your treatment temporarily or to stop it altogether.

A Changes in your skin during and after treatment

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

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
- 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.

Children and adolescents

Tafinlar is not intended for children and adolescents. The effects of Tafinlar in children and adolescents younger than 18 years old are not known.

1 Other medicines and Tafinlar

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 blood,
- such as gemfibrozil • some medicines used to treat certain psychiatric
- problems, such as haloperidol some antibiotics, such as clarithromycin,
- doxycyline and telithromycin some medicines for treating tuberculosis (TB),
- some medicines that reduce cholesterol levels, such as atorvastatin and simvastatin
- some immunosuppressants, such as cyclosporin,
- medicines that reduce stomach acid such as omeprazole
- some **anti-inflammatory** medicines, such as dexamethasone and methylprednisolone some medicines to treat HIV, such as ritonavir, amprenavir, indinavir, darunavir, delavirdine, efavirenz, fosamprenavir, lopinavir, nelfinavir,
- some medicines used for pain relief, such as fentanyl and methadone

tipranavir, saquinavir and atazanavir

 medicines to treat seizures (epilepsy), such as phenytoin, phenobarbital, primidone, valproic acid or carbamazepine

anti-depressant medicines such as nefazodone

and the herbal medicine St. John's wort (Hypericum) 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

Pregnancy, breast-feeding and fertility Tafinlar is not recommended during pregnancy.

show it to your doctor or pharmacist.

- 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 4 weeks after you stop taking it and for 4 months following the last dose of trametinib, when given in combination with
- 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 reliable method of birth control, such as a barrier method (e.g. condom), 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 breastfeeding.

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.

Pertility - 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 oharmacist.

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

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 according to the doctor's instructions.

Check with the doctor or pharmacist if you are uncertain. 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, 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. 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. How to take

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

Don't 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, or

 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 Don't take the morning and evening doses of Tafinlar at the same 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

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

as soon as you remember.

pharmacist advises you to.

times, as usual. Don't 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. Don't stop unless your doctor or

Do not take medicines in the dark! Check the label and the dose <u>each time</u> you take the 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 don't 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 missed doses and just take your next dose at your regular time:
- o if there are less than 6 hours until your next
- scheduled dose of Tafinlar, which is taken twice dailv. oif 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. 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

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
- red or black stools that look like tar

Fever

Taking Tafinlar may cause fever in more than 1 in 10 people. Tell your doctor immediately if you develop a fever (temperature 38.5°C or above) while you are taking this medicine. He will perform tests to find out if there are other causes for the four and will treat the problem.

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 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 If you notice any changes in your skin while taking this medicine, talk to your doctor or pharmacist as

soon as possible. Up to 1 in 10 people taking Tafinlar may 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 have scans of your chest and stomach area (called CT scans) regularly. You may have blood tests. These checks are to detect if any other cancer, including squamous cell carcinoma, develops inside your body. Pelvic examinations (for women) and analyse are also recommended before and at examinations are also recommended before and at

the end of your treatment. Check your skin regularly whilst taking this

medicine 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 get a skin rash while taking Tafinlar in combination with trametinib.

Eye problems Up to 1 in 100 people taking Tafinlar alone or in combination with trametinib can develop an eye problem called uveitis, which could damage your vision if it is not treated. Uveitis may develop rapidly

- and the symptoms include: eve 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, you develop signs and symptoms in your vision that include:

· loss of vision

blurred vision

- eye redness or itching
- colored dots in your vision halo (seeing blurred outlines around objects)
- 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. Other side effects

Besides the serious side effects mentioned above, people taking Tafinlar may also get other side effects. These include the following side effects: Very common side effects (may affect more

than 1 in 10 people): · Thickening of the outer layers of the skin

- · Skin effects such as rash, wart-like growths, or redness and swelling of the palms, fingers and feet (see 'Changes in your skin' earlier in section 4) Headache
- Decreased appetite Chills • Feeling weak Lack of energy

feet

Cough

• Nausea, vomiting, diarrhea

Unusual hair loss or thinning

• Fever (see 'Fever' earlier in section 4)

Common side effects (may affect up to 1 in 10 people): Constipation Flu-like illness

Low phosphorus in the blood, seen in blood tests

Increase in sugar (glucose) in the blood, seen in

· Joint pain, muscle pain, or pain in the hands or

• Changes in how the heart pumps blood

- in your skin' earlier in section 4) Uncommon side effects (may affect up to 1 in 100 people):
 - Inflammation of the eye (uveitis, see 'Eye problems' earlier in section 4)

Skin effects including rough scaly patches of skin, brown or yellowish thickening of the skin, benign skin tags (wart-like), dry skin, shiny bumps, open

sores, itching or redness of the skin (see 'Changes

- Inflammation of the pancreas (causing strong) abdominal pain)
- Inflammation of the fatty layer under the skin, symptoms include tender skin nodules
- Allergic reaction
- New melanoma • Kidney problems, kidney failure, seen in blood
- tests
- Disturbance in heart rhythm

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.

they get worse. Please read the trametinib package leaflet for details of the side effects you may get when

taking this medicine. The side effects that you may see when you take

Very common side effects (may affect more

- Fever
- · High blood pressure
- Stomach ache Nausea, vomiting
- Diarrhea Constination
- · Joint pain, muscle pain, or pain in the feet or
- Swelling of the feet or hands Nasal and throat inflammation

Bleeding Infection of the urinary system

Common side effects (may affect up to 1 in 10 people): Low blood pressure

 Excessive sweating Skin effects including rough scaly patches of skin, skin rash with pus-filled blisters, brown or yellowish thickening of the skin, skin tags, skin cracking, wart-like growths or redness and swelling of the wart-like growths or redness and swelling of the palms, feet and fingers, cutaneous squamous cell carcinoma (cuSCC - a type of skin cancer), inflammation of the fatty layer underneath the skin, papilloma (a type of skin tumor which is usually not harmful), infection of the skin (cellulitis),

Nail disorders such as nail bed changes, nail pain, infection and swelling of the cuticles

- Night sweats · Heart pumping less efficiently
- blood tests:
- and in a type of white blood cells (leukopenia) Low levels of sodium in the blood
- found mainly in heart, brain, and skeletal muscle
- Eye changes including swelling in the eye caused by fluid leakage (chorioretinopathy), inflammation
- · Kidney failure, inflammation of the kidneys • Inflammation of the lung (pneumonitis)

sight and reach of children and/or infants in order

5. HOW SHOULD THE MEDICINE BE STORED?

Do not use the medicine after the expiry date

• In addition to the active ingredient, the medicine also contains -

Black iron oxide (E172), shellac, propylene glycol.

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.

· Manufacturer: Glaxo Wellcome S.A., Burgos, Spain

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

than 1 in 10 people): Dizziness Chills

- Rash, dry skin, itching, acne-like problem Decreased appetite • Headache
- Cough
- Feeling tired, lack of energy
- Very common side effects that may show up in your blood tests:
- inflammation of hair follicles in the skin
- Dehydration (low levels of water or fluid) • Blurred vision, eyesight problems Shortness of breath

Unusual hair loss or thinning

- Muscle spasms Swelling of face
- Heart rate that is lower than the normal range and/or a decrease in heart rate Common side effects that may show up in your
- Decrease in number of red blood cells (anemia)
- by the liver
- Increase in blood sugar level
- Low levels of phosphate in the blood Uncommon side effects (may affect up to 1 in 100 people): Allergic reactions
- of the eye (uveitis), separation of the light-sensitive membrane at the back of the eye (the retina) from
 - · New primary melanoma 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.

homepage (www.health.gov.il) that directs you to the online form for reporting side effects, or by entering

 Low levels of white blood cells Abnormal blood test results related to the liver

· Sore mouth or mouth ulcers, inflammation of mucous membranes Dry mouth • Flu-like illness

 Increase in some substances (enzymes) produced Increase in creatine phosphokinase, an enzyme

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