Package leaflet: Information for the user

Modigraf 0.2 mg, granules for oral suspension
Modigraf 1 mg, granules for oral suspension
Tacrolimus

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Modigraf is and what it is used for

Modigraf contains the active substance tacrolimus. It is an immunosuppressant. Following your organ transplant (e.g. liver, kidney, heart), your body's immune system will try to reject the new organ. Modigraf is used to control your body's immune response enabling your body to accept the transplanted organ.

You may also be given Modigraf for an ongoing rejection of your transplanted liver, kidney, heart or other organ or if any previous treatment you were taking was unable to control this immune response after your transplantation.

Modigraf is used in adults and children.

2. What you need to know before you take Modigraf

Do not take Modigraf
- If you are allergic to tacrolimus or any of the other ingredients of this medicine (listed in section 6).
- If you are allergic to sirolimus (another substance used to prevent rejection of your transplanted organ) or to any macrolide antibiotic (e.g. erythromycin, clarithromycin, josamycin).

Warnings and precautions
Talk to your doctor or pharmacist before taking Modigraf

- if you have or have had liver problems.
- if you have diarrhoea for more than one day.
- if you feel strong abdominal pain accompanied or not with other symptoms, such as chills, fever, nausea or vomiting
- if you have an alteration of the electrical activity of your heart called "QT prolongation".

Tell your doctor immediately if during treatment you suffer from:

problems with your vision such as blurred vision, changes in colour vision, difficulty in seeing detail or if your field of vision becomes restricted.

Your doctor may need to adjust your dose of Modigraf.

You should keep in regular contact with your doctor. From time to time, your doctor may need to do blood, urine, heart, eye tests, to set the right dose of Modigraf.

You should limit your exposure to the sun and UV (ultraviolet) light whilst taking Modigraf. This is because immunosuppressants like Modigraf could increase the risk of skin cancer. In case of sun exposure, wear appropriate protective clothing and use a sunscreen with a high sun protection factor.

Other medicines and Modigraf
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

It is not recommended that Modigraf is taken with ciclosporin (another medicine used for the prevention of transplant organ rejection).

Modigraf blood levels can be affected by other medicines you take, and blood levels of other medicines can be affected by taking Modigraf, which may require interruption, an increase or a decrease in Modigraf dose. In particular, you should tell your doctor if you are taking or have recently taken medicines like:
- antifungal medicines and antibiotics, particularly so-called macrolide antibiotics, used to treat infections e.g. ketoconazole, fluconazole, itraconazole, voriconazole, clotrimazole, and isavuconazole, erythromycin, clarithromycin, josamycin, and rifampicin
- HIV protease inhibitors (e.g. ritonavir, nelfinavir, saquinavir), the booster medicine cobicistat, and combination tablets, used to treat HIV infection
- HCV protease inhibitors (e.g. telaprevir, boceprevir, and the combination ombitasvir/paritaprevir/ritonavir with or without dasabuvir), used to treat hepatitis C infection
- nilotinib and imatinib (used to treat certain cancers)
- mycophenolic acid, used to suppress the immune system to prevent transplant rejection
- medicines for stomach ulcer and acid reflux (e.g. omeprazole, lansoprazole or cimetidine)
- anti-emetics, used to treat nausea and vomiting (e.g. metoclopramide)
- cisapride or the antacid magnesium-aluminium-hydroxide, used to treat heartburn
- the contraceptive pill, hormone treatments with ethinylestradiol, or hormone treatments with danazol
- medicines used to treat high blood pressure or heart problems (e.g. nifedipine, nicardipine, diltiazem and verapamil)
- anti-arrhythmic medicines (amiodarone) used to control arrhythmia (uneven beating of the heart)
- medicines known as “statins” used to treat elevated cholesterol and triglycerides
- phenytoin or phenobarbital, used to treat epilepsy
- the corticosteroids prednisolone and methylprednisolone, belonging to the class of corticosteroids used to treat inflammations or suppress the immune system (e.g. in transplant rejection)
- nefazodone, used to treat depression
- Herbal preparations containing St. John’s Wort (*Hypericum perforatum*) or extracts of *Schisandra sphenanthera*.

Tell your doctor if you are taking or need to take ibuprofen (used to treat fever, inflammation and pain), amphotericin B (used to treat bacterial infections) or antivirals (used to treat viral infections e.g. aciclovir). These may worsen kidney or nervous system problems when taken together with Modigraf.

Your doctor also needs to know if you are taking potassium supplements or certain diuretics used for heart failure, hypertension and kidney disease, (e.g. amiloride, triamterene, or spironolactone), non-steroidal anti-inflammatory drugs (NSAIDs, e.g. ibuprofen) used for fever, inflammation and pain, anticoagulants (blood thinners), or oral medicines for diabetes, while you take Modigraf.

If you need to have any vaccinations, please tell your doctor before.

Modigraf with food and drink
You should generally take Modigraf on an empty stomach or at least 1 hour before or 2 to 3 hours after a meal. Grapefruit and grapefruit juice should be avoided while taking Modigraf, since it can affect its levels in the blood.

Pregnancy and breast-feeding
If you take Modigraf during pregnancy, it may pass into your baby through the placenta. It could potentially influence the health of the baby or adversely influence the course of the pregnancy.
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
Modigraf passes into breast milk. Therefore, you should not breast-feed whilst using Modigraf.

Driving and using machines
Do not drive or use any tools or machines if you feel dizzy or sleepy, or have problems seeing clearly after taking Modigraf. These effects are more frequent if you also drink alcohol.

Modigraf contains lactose
Modigraf contains lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. How to take Modigraf

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure. Modigraf should be prescribed by doctors trained to treat transplant patients and experienced in the use of medicines that control the body's immune system (immunosuppressants).

Make sure that you receive the same tacrolimus medicine every time you collect your prescription, unless your transplant specialist has agreed to change to a different tacrolimus medicine.

This medicine should be taken twice a day. If the physical appearance has changed from the normal white granules, or if dose instructions have changed, speak to your doctor or pharmacist as soon as possible to make sure that you have the right medicine.

The starting dose to prevent the rejection of your transplanted organ will be determined by your doctor calculated according to your body weight. Initial doses just after transplantation will generally be in the range of 0.075 - 0.30 mg per kg body weight per day depending on the transplanted organ. When treating rejection, these same doses may be used.

Your dose depends on your general condition and on which other immunosuppressive medicines you are taking.

Children and adolescents
Children and adolescents will receive doses of Modigraf calculated in the same way as adults. In general children need higher doses per kg of body weight to achieve the same effective levels in the blood as adults.

Following the initiation of your treatment with Modigraf, frequent blood tests will be taken by your doctor to define the correct dose and to adjust the dose from time to time. Your doctor will usually

reduce your Modigraf dose once your condition has stabilised. Your doctor will tell you exactly how many sachets to take.

You will need to take Modigraf every day as long as you need immunosuppression to prevent rejection of your transplanted organ. You should keep in regular contact with your doctor.

Modigraf is taken orally twice daily, usually in the morning and evening. Take Modigraf on an empty stomach or 2 to 3 hours after a meal. Wait at least 1 hour until the next meal.

How to prepare the Modigraf sachets for use?
Your doctor will advise you on the number of sachets that you need to open and the volume of water that is required to make a suspension. For accurate measuring the volume of water you can use a syringe or graduated cylinder.

Pour the prescribed volume of water (at room temperature) into a glass or cup, up to a maximum of 50 ml. Place the cup with water on a stable surface. Do not use cups or spoons that are made of PVC (polyvinylchloride) to take Modigraf because the active substance in Modigraf may stick to PVC. Carefully open the prescribed number of sachets, e.g. with a pair of scissors at the point indicated with an arrow. Hold the opened sachet between thumb and index finger above the cup with the open side of the sachet facing downwards. Gently tap on the closed end of the sachet and pour the contents of each sachet into the glass or cup containing the water. Do not use any utensils or liquids to empty the sachet. If you follow these instructions, you will get the right amount of granules from the sachet. It is normal that some granules stay behind; the sachet was designed that way.
Stir, or swirl gently until the granules have been suspended completely. The suspension can be drawn up with a syringe or swallowed directly by the patient. The liquid has a sweet taste. Rinse the glass or cup once with the same amount of water and drink this, too. The liquid should be drunk immediately after preparation.

If you take more Modigraf than you should
If you have accidentally taken too much Modigraf, contact your doctor or nearest hospital emergency department immediately.

If you forget to take Modigraf
Do not take a double dose to make up for forgotten individual doses.
If you have forgotten to take your Modigraf, wait until it is time for the next dose, and then continue as before.

If you stop taking Modigraf
Stopping your treatment with Modigraf may increase the risk of rejection of your transplanted organ. Do not stop your treatment unless your doctor tells you to do so.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Modigraf reduces your body's defence mechanism (immune system), which will not be as good at fighting infections. Therefore, you may be more prone to infections while you are taking Modigraf.

Severe effects may occur, including allergic and anaphylactic reactions (a very serious type of allergic reaction with fainting and difficulty breathing, which needs immediate medical attention). Benign and malignant tumours have been reported following Modigraf treatment.

Cases of pure red cell aplasia (a very severe reduction in red blood cell counts), agranulocytosis (a severely lowered number of white blood cells) and haemolytic anaemia (decreased number of red

blood cells due to abnormal breakdown) have been reported. It is not known exactly how often these side effects occur.

Very common side effects (may affect more than 1 in 10 people):
- Increased blood sugar, diabetes mellitus, increased potassium in the blood
- Difficulty in sleeping
- Trembling, headache
- Increased blood pressure
- Liver function tests abnormal
- Diarrhoea, nausea
- Kidney problems

Common side effects (may affect up to 1 in 10 people):
- Reduction in blood cell counts (platelets, red or white blood cells), increase in white blood cell counts, changes in red blood cell counts (seen in blood tests)
- Reduced magnesium, phosphate, potassium, calcium or sodium in the blood, fluid overload, increased uric acid or lipids in the blood, decreased appetite, increased acidity of the blood, other changes in the blood salts (seen in blood tests)
- Anxiety symptoms, confusion and disorientation, depression, mood changes, nightmare, hallucination, mental disorders
- Fits, disturbances in consciousness, tingling and numbness (sometimes painful) in the hands and feet, dizziness, impaired writing ability, nervous system disorders
- Blurred vision, increased sensitivity to light, eye disorders
- Ringing sound in your ears
- Reduced blood flow in the heart vessels, faster heartbeat
- Bleeding, partial or complete blocking of blood vessels, reduced blood pressure
- Shortness in breath, changes in the lung tissue, collection of liquid around the lung, inflammation of the throat, cough, flu-like symptoms
- Stomach problems such as inflammation or ulcer causing abdominal pain or diarrhoea, bleeding in the stomach, inflammation or ulcer in the mouth, collection of fluid in the belly, vomiting, abdominal pain, indigestion, constipation, passing wind, bloating, loose stools
- Bile duct disorders, yellowing of the skin due to liver problems, liver tissue damage and inflammation of the liver
- Itching, rash, hair loss, acne, increased sweating
- Pain in joints, limbs, back and feet, muscle spasms
- Insufficient function of the kidneys, reduced production of urine, impaired or painful urination
- General weakness, fever, collection of fluid in your body, pain and discomfort, increase of the enzyme alkaline phosphatase in your blood, weight gain, feeling of temperature disturbed
- Insufficient function of your transplanted organ

Uncommon side effects (may affect up to 1 in 100 people):
- Changes in blood clotting, reduction in the number of all types of blood cells (seen in blood tests)
- Dehydration, inability to urinate
- Abnormal blood test results: reduced protein or sugar, increased phosphate, increase of the enzyme lactate dehydrogenase
- Coma, bleeding in the brain, stroke, paralysis, brain disorder, speech and language abnormalities, memory problems
- Clouding of the eye lens, impaired hearing
- Irregular heartbeat, stop of heartbeat, reduced performance of your heart, disorder of the heart muscle, enlargement of the heart muscle, stronger heartbeat, abnormal ECG, heart rate and pulse abnormal
- Blood clot in a vein of a limb, shock
- Difficulties in breathing, respiratory tract disorders, asthma
- Obstruction of the gut, increased blood level of the enzyme amylase, reflux of stomach content in your throat, delayed emptying of the stomach
- Inflammation of the skin, burning sensation in the sunlight

- Joint disorders
- Painful menstruation and abnormal menstrual bleeding
- Multiple organ failure, flu-like illness, increased sensitivity to heat and cold, feeling of pressure on your chest, jittery or abnormal feeling, weight loss

Rare side effects (may affect up to 1 in 1,000 people):
- Small bleedings in your skin due to blood clots
- Increased muscle stiffness
- Blindness, deafness
- Collection of fluid around the heart
- Acute breathlessness
- Cyst formation in your pancreas
- Problems with blood flow in the liver
- Serious illness with blistering of skin, mouth, eyes and genitals; increased hairiness
- Thirst, fall, feeling of tightness in your chest, decreased mobility, ulcer

Very rare side effects (may affect up to 1 in 10,000 people):
- Muscular weakness
- Abnormal heart scan
- Liver failure
- Painful urination with blood in the urine
- Increase of fat tissue

Not known (frequency cannot be estimated from the available data):
- Abnormality of the optic nerve (optic neuropathy)

Children and adolescents
Children and adolescents may experience the same side effects as adults.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly (for details see below). By reporting side effects, you can help provide more information on the safety of this medicine.

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Website: www.moh.gov.cy/phs

5. How to store Modigraf

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and sachet after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special temperature storage conditions.

After preparation, the suspension should be taken immediately.

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. Contents of the pack and other information

What Modigraf contains
- The active substance is tacrolimus.
  Each sachet of Modigraf 0.2 mg granules contains 0.2 mg of tacrolimus (as monohydrate).
  Each sachet of Modigraf 1 mg granules contains 1 mg of tacrolimus (as monohydrate).
- The other ingredients are: lactose monohydrate, hypromellose (E464) and croscarmellose sodium (E468).

What Modigraf looks like and contents of the pack
Modigraf granules for oral suspension are white granules supplied in sachets.
Packs containing 50 sachets are available.

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Manufacturer
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Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu/.