EMA/322302/2014

# Summary of the risk management plan (RMP) for Envarsus (tacrolimus)

This is a summary of the risk management plan (RMP) for Envarsus, which details the measures to be taken in order to ensure that Envarsus is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Envarsus, which can be found on Envarsus' EPAR page.

## Overview of disease epidemiology

Envarsus is a medicine given to adults to help prevent the body's immune system from attacking and rejecting a transplanted kidney or liver. It can also be given to treat an ongoing rejection, when previous treatment has failed.

Although the number of organ transplants carried out in the European Union (EU) varies quite significantly from country to country, on average about 14 organ transplantation procedures are performed per million people per year. Around 70% of these (about 15,000 in the EU) are kidney transplants and another 20% are liver transplants. Worldwide, at the end of 2003 approximately 400,000 patients were living with a kidney transplant, and this number has steadily increased since 1990. Nearly all people who receive a transplanted organ will require lifelong treatment to prevent rejection.

## Summary of treatment benefits

Envarsus is a medicine that contains the active substance tacrolimus. It is similar to a reference medicine called Advagraf that also contains tacrolimus, but Envarsus has been formulated in a different way and is available at different doses. Envarsus is available as prolonged-released tablets (tablets that allow tacrolimus to be released slowly from the tablet over several hours and in a form that the body can absorb easily). It is taken once a day.

Envarsus has been investigated in 24 clinical studies involving over 1,000 people, including healthy volunteers, adult kidney transplant patients and adult liver transplant patients. In addition, as medicines containing tacrolimus have been used for almost 20 years, results of studies and experiences with other tacrolimus medicines have been taken into account during the evaluation of Envarsus.

Envarsus has been shown to be at least as effective as Prograf, an immediate-release tacrolimus medicine (one that releases tacrolimus more quickly), in two main studies in patients with kidney transplants. The main measure of effectiveness in both studies was the number of patients who had treatment failure (death, failure or rejection of the transplanted organ, or loss of the patient from follow-up) after 12 months.

The first study involved 326 patients who had already had a kidney transplant and were being treated with Prograf and other immunosuppressants to prevent rejection. Patients were either switched to

treatment with Envarsus once daily or continued Prograf treatment twice daily. Failure rates were 2.5% in both groups (4 of 162 patients treated with Envarsus, and 4 of 162 treated with Prograf). The second study compared Envarsus with Prograf as part of standard treatment in 543 patients with a newly transplanted kidney. Treatment failure occurred in 18.3% patients treated with Envarsus (49 out of 268), and 19.6% given Prograf (54 out of 257).

The company also provided studies on the levels of tacrolimus in the body after taking Envarsus, which showed that it produced levels of tacrolimus that have been previously shown to be effective in treating and preventing rejection, and reported results in 29 patients who were given Envarsus starting after a liver transplant, none of whom rejected the transplanted organ during the 360 days following transplantation.

## Unknowns relating to treatment benefits

There is only limited evidence from studies as to the appropriate dose of Envarsus in non-white patients. Compared with white patients, black patients may need higher tacrolimus doses for the medicine to work properly.

## Summary of safety concerns

***Important identified risks***

| Risk | What is known | Preventability |
|---|---|---|
| Altered blood levels of tacrolimus when other medicines are taken (interaction with other medication) | Some other medicines, (particularly medicines that react with an enzyme called CYP3A4), including over-the-counter and herbal medicines, may increase or decrease the blood levels of tacrolimus and so affect its action or the risk of side effects. | Care is needed when administering tacrolimus with other medicines, particularly those listed in the product information, and patients must tell their doctors if they are taking or plan to take other medicines. Tacrolimus blood levels should be regularly checked and adjusted to make sure that there is the correct level of tacrolimus in the patient's blood, particularly when taking other medicines. |
| High blood pressure (hypertension) | Patients with high blood pressure are at greater risk of developing heart problems associated with the tacrolimus treatment. | Blood pressure should be monitored regularly during the period just after transplantation, and a change in treatment should be considered if significant increases in blood pressure occur. |
| Problems with the nervous system or eyes (neurological and visual disorders) | Medicines containing tacrolimus can produce side effects affecting the nervous system such as headache and tremor (shaking), which are known to occur in more than 1 patient in 10, while problems | Eye tests and tests to check the normal functioning of the nervous system should be carried out regularly during the period just after |

| Risk | What is known | Preventability |
|---|---|---|
| | such as dizziness, pins and needles (paraesthesia), altered sensation (dysaesthesia), fits (seizures) may occur in up to one patient in 10. They can also produce effects on the eyes such as blurred vision and inability to bear bright light (photophobia). | transplantation, and a change in treatment should be considered if significant problems occur. |
| Posterior reversible encephalopathy syndrome | Patients treated with tacrolimus have been reported to develop posterior reversible encephalopathy syndrome (PRES), a rare nervous system disorder involving an increase in blood pressure, headaches, abnormal mental state, seizures and vision loss. | If patients taking tacrolimus have any symptoms of PRES, a radiological scan (e.g. MRI) should be performed. If PRES is diagnosed, the symptoms should be treated and the use of tacrolimus should be stopped immediately. Most patients completely recover. |
| Effects on control of blood sugar (diabetogenicity) | Tacrolimus-containing medicines very commonly cause high blood sugar levels and diabetes (in more than 1 patient in 10). | Blood sugar levels should be monitored regularly during the period just after transplantation, and a change in treatment should be considered if significant problems occur. |
| Changes in levels of salts (electrolytes) in the blood | Patients taking medicines that contain tacrolimus may have changes in the levels of various electrolytes in their blood. In particular, more than 1 patient in 10 may have increased levels of potassium. | Electrolytes (particularly potassium) in the blood should be monitored regularly during the period just after transplantation, and a change in treatment should be considered if significant problems occur. |
| Liver function problems (hepatic dysfunction) | In patients whose liver does not work properly, blood levels of tacrolimus may change significantly. | In patients with hepatic dysfunction reduced doses of tacrolimus may be needed and levels of tacrolimus in the blood should be carefully checked and adjusted. |
| Kidney function problems (renal dysfunction) | Reduced kidney function occurs in more than 1 patient in 10 taking tacrolimus. | Kidney function should be monitored carefully in patients taking tacrolimus. |
| Changes in blood cell counts | Changes in blood cell counts are seen in up to 1 patient in 10 treated with tacrolimus. | Blood cell counts should be carried out regularly during the period just after transplantation, and a change in treatment should be considered if significant problems occur. |
| Pure red cell aplasia | Cases of pure red cell aplasia (PRCA) have | Warnings and precautionary |

| Risk | What is known | Preventability |
|---|---|---|
| (a type of anaemia affecting red blood cells only) | been reported in patients treated with tacrolimus. However, all of the patients had other risk factors (e.g. because they had an infection with a virus called parvovirus B19, or had an underlying disease or were taking other medicines thought to lead to PRCA). | information are provided in the product information. |
| Problems with blood clotting (coagulopathies) | Coagulopathies occur uncommonly (in up to 1 patient in 100) in patients treated with tacrolimus. | Blood clotting should be monitored regularly during the period just after transplantation, and a change in treatment should be considered if significant problems occur. |
| Medication errors | Envarsus and other medicines containing tacrolimus are <u>not</u> interchangeable. Mistakes such as inadvertently changing the type of tacrolimus medicine (e.g. swapping a once-daily medicine for a twice-daily medicine), have occurred with tacrolimus medicines, and can lead to toxicity or rejection of the transplanted organ. The risk of inadvertent use of the wrong form of tacrolimus is increased by the co-existence of numerous products. | Warning and precautionary information about medication errors is provided in the product information. If a prescriber considers that switching a patient to a different tacrolimus product would be of benefit, the change requires careful supervision and monitoring by an appropriate specialist.<br>Additional means of alerting healthcare professionals and patients to the risks (educational materials and measures such as patient cards) will be agreed as appropriate at national level with the national competent authorities. |
| Diarrhoea | If patients experience episodes of diarrhoea, blood levels of tacrolimus may change significantly. | In case of diarrhoea, the patient's tacrolimus blood levels should be checked and adjusted to make sure that there is the correct level of tacrolimus in the patient's blood. Patients who have diarrhoea for more than one day should speak to their doctor. |
| Problems with the stomach and intestines (gastrointestinal disorders) | Problems affecting the gut, including ulcers, have been reported in transplant patients including those on tacrolimus. Symptoms reported include nausea (feeling sick) and diarrhoea, which may occur in more than one patient in 10. | Patients should be monitored for more serious gastrointestinal problems such as ulcers. |

| Risk | What is known | Preventability |
|---|---|---|
| Heart problems (cardiac disorders) | Although uncommon (seen in less than one patient in 100), enlargement of some parts of the heart has been seen in patients treated with tacrolimus. Most cases have been reversible, and have been caused by very high blood levels of tacrolimus. The risk may be increased by heart disease, use of corticosteroid medicines, high blood pressure, poor kidney or liver function, infections, fluid overload and oedema (fluid build-up in the body).<br>Tacrolimus may also alter the electrical activity of the heart (prolonged QT interval) and may be associated with irregular heart rhythm (arrhythmias). | High-risk patients should be monitored using scans (echocardiography) or checks on the electrical activity of the heart (ECG). If these become abnormal, the tacrolimus dose can be lowered, or another immunosuppressive medicine can be used.<br>Tacrolimus should be given with extra care to patients who have or are suspected to have an inborn problem with the electrical activity of the heart called 'congenital long QT syndrome'. |
| Disorders where too many white blood cells are produced (lymphoproliferative disorders) | Patients treated with tacrolimus have been reported to develop lymphoproliferative disorders including a type associated with infection with a virus called EBV (Epstein Barr virus). The risk of this is higher when patients need a combination of other immunosuppressive medicines with tacrolimus. | Infection with EBV should be checked before starting treatment with Envarsus. During treatment, careful monitoring for EBV is recommended. |
| Cancer (neoplasms) | As with other immunosuppressant medicines, patients are at increased risk of developing cancer, including skin cancer, as well as benign growths. | Because of the potential risk of cancerous skin changes, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor. |
| Unusual infections due to a weakened immune system (opportunistic infections) | Patients treated with any immunosuppressants are at increased risk of opportunistic infections to which they would normally be resistant. Some of these infections (e.g. BK virus, which can affect the kidney, and JC virus, which affects the brain and nervous system) may lead to serious or fatal conditions. | Opportunistic infections should be considered by healthcare professionals if immunosuppressed patients have worsening kidney function or signs of nervous system problems. |
| Use in pregnant or breastfeeding women | There have not been any studies in pregnant or breastfeeding women.<br>However, it is known that the risk of side effects or risk to the pregnancy is not worse with tacrolimus compared with other immunosuppressants. Tacrolimus treatment can be considered in pregnant women when there is no safer alternative, and when it is judged to be necessary. There is a risk of | Information and warnings on the use of tacrolimus during pregnancy and breastfeeding is discussed in the product label and patient information leaflet.<br>If pregnant women take tacrolimus, the newborn should be monitored for side effects (especially effects on the |

| Risk | What is known | Preventability |
|---|---|---|
| | premature delivery (delivery of the baby before 37 weeks) as well as hyperkalaemia (high levels of blood potassium which can cause abnormal heart rhythm), but this should become normal when stopping treatment.<br>Tacrolimus can pass to the baby through breast milk. | kidneys).<br>Women should not breastfeed while receiving tacrolimus. |

***Important potential risks***

| Risk | What is known |
|---|---|
| Use outside the licensed conditions (off-label use) | There is a potential risk that Envarsus prolonged-release tablets may be used outside the licensed indications, for example in uses for which other tacrolimus medicines are licensed or in other patient groups than those for whom it is approved. |

***Missing information***

| Risk | What is known |
|---|---|
| Use in children | In general, children need relatively higher tacrolimus doses than adults to achieve similar blood concentrations. Envarsus prolonged-release tablets have not been studied in children, and should not be used in children. |

## Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Envarsus can be found on Envarsus' EPAR page.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published on Envarsus's EPAR page; how they are implemented in each country however will depend upon agreement between the marketing authorisation holder and the national authorities.

These additional risk minimisation measures are for the following risks:

***Medication errors***

| |
|---|
| **Risk minimisation measure**: Educational program |
| Objective and rationale: to reduce the risk of medication errors by informing healthcare professionals and patients of this risk and how to minimise it |
| Description: Various educational programs will be initiated across the EU to inform healthcare professionals and patients about the risk of medication errors and measures that they should take to minimise this risk. These may include the use of patient cards and special information (educational materials) to healthcare professionals (doctors and pharmacists).<br>Routine ongoing safety monitoring of medication errors by the company responsible for Envarsus will also continue and the company will give regular feedback to EU health authorities. Where medication errors are detected, special measures will be undertaken as necessary to minimise risks to patients. These measures may include additional information and advice as necessary based on experience with the product on the market. |

## Planned post-authorisation development plan

The active substance in Envarsus, tacrolimus, has been used in organ transplantation in many countries worldwide for about 20 years. No specific clinical studies are planned for Envarsus after it has been approved for use.

***Studies which are a condition of the marketing authorisation***

None.

## Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 06-2014.