

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

TYSABRI 300 mg concentrate for solution for infusion natalizumab

Read all of this leaflet carefully before you start using this medicine.

In addition to this leaflet you will be given a Patient Alert Card, which contains important safety information that you need to know before you are given TYSABRI (pronounced tie-SA-bree) and during treatment with TYSABRI.

- Keep this leaflet and the Patient Alert Card. You may need to read them again.
- It is important that you keep the Alert Card with you during treatment and for six months after the last dose of TYSABRI, since side effects may occur even after you have stopped treatment.
- If you have any further questions, ask your doctor or pharmacist.
- This leaflet will explain about side effects that some patients experience on TYSABRI. If you have any worrying side effects, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

In this leaflet:

1. What TYSABRI is and what it is used for
2. Before you use TYSABRI
3. How to use TYSABRI
4. Possible side effects
5. How to store TYSABRI
6. Further information

1. WHAT TYSABRI IS AND WHAT IT IS USED FOR

TYSABRI is used to treat multiple sclerosis (MS).

The symptoms of MS vary from patient to patient, and you may experience some or none of them. Symptoms can include; walking problems, numbness in the face, arms or legs, problems seeing things, tiredness, feeling off-balance or light headed, bladder and bowel problems, difficulty in thinking and concentrating, depression, acute or chronic pain, sexual problems, and stiffness and muscle spasms. When the symptoms flare up, it is called a relapse (also known as an exacerbation or an attack). When a relapse occurs, you may notice the symptoms suddenly, within a few hours, or slowly progressing over several days. Your symptoms will then usually improve gradually (this is called a remission).

MS causes inflammation in the brain that damages the nerve cells. In TYSABRI the active ingredient is natalizumab, a protein similar to your own antibodies. It stops the cells that cause inflammation from going into your brain. This reduces nerve damage caused by MS.

In clinical trials, TYSABRI approximately halved the progression of the disabling effects of MS and also decreased the number of MS attacks by about two-thirds. However, TYSABRI cannot repair the damage that has already been caused by MS. When you receive TYSABRI you might not notice any improvement, but TYSABRI may still be working to prevent your MS becoming worse.

It is important to continue with your medicine for as long as you and your doctor decide that it is helping you.

2. BEFORE YOU USE TYSABRI

Before you start treatment with TYSABRI, it is important that you and your doctor have discussed the benefits you would expect to receive from this treatment and the risks that are associated with it.

Do not use TYSABRI

- If you are allergic (hypersensitive) to natalizumab or any of the other ingredients of TYSABRI (see section 6 for the ingredients).
- If your doctor has told you that you have PML (progressive multifocal leukoencephalopathy). PML is a rare infection of the brain.
- If your doctor tells you that you have a serious problem with your immune system (due to disease for example, leukaemia or HIV or due to a medicine you are taking or have previously taken).
- If you are taking medicines that cannot be used with TYSABRI (see Using other medicines, below).
- If you have cancer (unless it is a type of skin cancer called basal cell carcinoma).
- If you are under 18 years of age.

Take special care with TYSABRI

There have been cases of a rare brain infection called PML (progressive multifocal leukoencephalopathy) that have occurred in patients who have been given TYSABRI. PML may lead to severe disability or death. The risk of PML appears to increase the longer that you are on treatment especially if you have been on treatment for more than two years. It is not known if the chance of getting PML continues to rise, remains the same, or falls after you have been on TYSABRI for more than three years. In patients with PML a reaction known as IRIS (Immune Reconstitution Inflammatory Syndrome) is likely to occur after treatment for PML, as TYSABRI is removed from your body. IRIS may lead to your condition getting worse, including worsening of brain function.

The symptoms of PML may be similar to an MS relapse (e.g. weakness or visual changes). Therefore, if you believe your MS is getting worse or if you notice any new symptoms, it is very important that you speak to your doctor as soon as possible.

Speak with your partner or caregivers and inform them about your treatment. Symptoms might arise that you might not become aware of by yourself, such as changes in mood or behaviour, memory lapses, speech and communication difficulties, which your doctor may need to investigate further to rule out PML.

You will also find this information in the Patient Alert Card you have been given by your doctor. It is important that you keep this Alert Card and show it to your partner or caregivers.

Serious infections may occur with TYSABRI. If you develop any infection, or if you develop symptoms like an unexplained fever, severe diarrhoea, prolonged dizziness / headache / stiff neck, weight loss, or listlessness, or other symptoms potentially associated with an infection whilst receiving TYSABRI, speak to your doctor as soon as possible and show the Patient Alert Card and this package leaflet to him.

You will also find this information in the Patient Alert Card you have been given by your doctor. It is important that you keep this Alert Card.

Using other medicines

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines you may have obtained without a prescription. You may not be able to use TYSABRI with some medicines that affect your immune system.

Pregnancy and breast-feeding

You should not use TYSABRI if you are pregnant unless you have discussed this with your doctor. Be sure to tell your doctor immediately if you are pregnant, think you may be pregnant, or if you are planning to become pregnant.

Do not breast-feed whilst using TYSABRI. You should discuss with your doctor whether you choose to breast-feed or to use TYSABRI.

Ask your doctor or pharmacist for advice before taking any other medicine with TYSABRI.

Driving and using machines

TYSABRI is not expected to have an effect on your ability to drive or to operate machines. If you are concerned, discuss this with your doctor.

3. HOW TO USE TYSABRI

TYSABRI will be prepared and given to you by a doctor.

Information for medical or healthcare professionals on how to prepare and administer TYSABRI is provided at the end of this leaflet.

The adult dose is 300 mg given once every 4 weeks.

TYSABRI must be diluted before it is given to you. It is given as a drip into a vein (by intravenous infusion), usually in your arm. This takes about 1 hour.

A few patients have had an allergic reaction to TYSABRI. Your doctor will check for allergic reactions during the infusion and for 1 hour afterwards.

It is important to continue with your medicine for as long as you and your doctor decide that it is helping you. Continuous dosing with TYSABRI is important, especially during the first few months of treatment. This is because patients who received one or two doses of TYSABRI and then had a gap in treatment of three months or more, were more likely to have an allergic reaction when resuming treatment.

If you miss your dose of TYSABRI

If you miss your usual dose of TYSABRI, arrange with your doctor to receive it as soon as you can. You can then continue to receive your dose of TYSABRI every 4 weeks.

4. POSSIBLE SIDE EFFECTS

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

If you have any worrying side effects, including any not listed in this leaflet, please tell your doctor, nurse or pharmacist as soon as possible.

Speak to your doctor or nurse immediately if you notice any of the following:

Signs of allergy to TYSABRI, during or shortly after your infusion:

- Itchy rash (hives)
- Swelling of your face, lips or tongue
- Difficulty breathing
- Chest pain or discomfort
- Increase or decrease in your blood pressure (your doctor or nurse will notice this if they are monitoring your blood pressure).

Signs of a possible liver problem:

- Yellowing of your skin or the whites of your eyes
- Unusual darkening of the urine.

TYSABRI can also have other side effects.

Side effects are listed below by how commonly they have been reported in clinical trials:

Common side effects that may occur in less than 10 in 100 patients:

- Urinary tract infection
- Sore throat and runny or blocked up nose
- Shivering
- Itchy rash (hives)
- Headache
- Dizziness
- Feeling sick (nausea)
- Being sick (vomiting)
- Joint pain
- Fever
- Tiredness.

Uncommon side effects that may occur in less than 1 in 100 patients:

- Severe allergy (hypersensitivity).

Rare side effects that may occur in less than 1 in 1000 patients:

- Unusual infections (so-called “Opportunistic infections”)
- Progressive multifocal leukoencephalopathy (PML), a rare brain infection.

What to do if your MS gets worse or you notice new symptoms

There have been reports of a rare brain infection called PML (progressive multifocal leukoencephalopathy) that have occurred in patients who have been given TYSABRI. PML usually leads to severe disability or death.

The symptoms of PML may be similar to an MS relapse.

- Therefore, if you believe your MS is getting worse or if you notice any new symptoms, it is important that you speak to your doctor as soon as possible.
- Discuss your treatment with your partner or caregivers. They might see new symptoms that you might not notice such as changes in mood or behaviour, memory lapses, speech and communication difficulties, which your doctor may need to investigate further to rule out PML.
- Show the Alert Card and this package leaflet to any doctor involved with your treatment, not only to your neurologist.

Serious infections may occur with TYSABRI. The symptoms of infections include:

- an unexplained fever
- severe diarrhoea

- shortness of breath
 - prolonged dizziness
 - headache
 - stiff neck
 - weight loss
 - listlessness.
- Speak to your doctor as soon as possible if you think you have an infection.
 - Show the Alert Card and this package leaflet to any doctor involved with your treatment, not only to your neurologist.

You will also find this information in the Patient Alert Card you have been given by your doctor.

Will TYSABRI always work?

In a few patients who use TYSABRI, over time the body's natural defence may stop TYSABRI from working properly (the body develops antibodies to TYSABRI). Your doctor can decide whether TYSABRI is not working properly for you by testing your blood and will stop TYSABRI, if necessary.

5. HOW TO STORE TYSABRI

Keep out of the reach and sight of children.

Unopened vial:

Store in a refrigerator (2°C to 8°C).

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

Do not use TYSABRI after the expiry date stated on the label and carton.

Diluted solution:

After dilution, immediate use is recommended. If not used immediately, the diluted solution must be stored at 2°C - 8°C and infused within 8 hours of dilution.

Do not use TYSABRI if you notice particles in the liquid and/or the liquid in the vial is discoloured.

6. FURTHER INFORMATION

What TYSABRI contains

Each 15 ml vial of concentrate contains 300 mg natalizumab (20 mg/ml).

The other ingredients are:

Sodium phosphate, monobasic, monohydrate

Sodium phosphate, dibasic, heptahydrate

Sodium chloride

Polysorbate 80 (E433)

Water for injections.

What TYSABRI looks like and contents of the pack

TYSABRI is a clear, colourless to slightly cloudy liquid. Each carton contains one glass vial.

TYSABRI must be diluted before it is given to you.

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For any further information about this medicine, please contact the local representative of the Marketing Authorisation Holder. This information is provided at the end of the leaflet.

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This leaflet was last approved in 05/2010.

Detailed information on this medicine is available on the European Medicines Agency (EMA) web site: <http://www.emea.europa.eu/>.

The following information is intended for medical or healthcare professionals only:

1. Inspect the TYSABRI vial for particles prior to dilution and administration. If particles are observed and/or the liquid in the vial is not colourless, clear to slightly opalescent, the vial must not be used.
2. Use aseptic technique when preparing TYSABRI solution for intravenous (IV) infusion. Remove flip-top from the vial. Insert the syringe needle into the vial through the centre of the rubber stopper and remove 15 ml concentrate for solution for infusion.
3. Add the 15 ml concentrate for solution for infusion to 100 ml sodium chloride 9 mg/ml (0.9%) solution for injection. Gently invert the TYSABRI solution to mix completely. Do not shake.
4. TYSABRI must not be mixed with other medicinal products or diluents.
5. Visually inspect the diluted product for particles or discolouration prior to administration. Do not use if it is discoloured or if foreign particles are seen.
6. The diluted product is to be used as soon as possible and within 8 hours of dilution. If the diluted product is stored at 2°C - 8°C (do not freeze), allow the solution to warm to room temperature prior to infusion.
7. The diluted solution is to be infused intravenously over 1 hour at a rate of approximately 2 ml/minute.

8. After the infusion is complete, flush the intravenous line with sodium chloride 9 mg/ml (0.9%) solution for injection.
9. Each vial is for single-use only.
10. Any unused product or waste material must be disposed of in accordance with local requirements.