Package leaflet: Information for the patient

Tysabri 300 mg concentrate for solution for infusion
natalizumab

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

In addition to this leaflet you will be given a patient alert card. This contains important safety information that you need to know before and during treatment with Tysabri.

- Keep this leaflet and the patient alert card. You may need to read them again. Keep the leaflet and patient alert card with you during treatment and for six months after the last dose of this medicine , as side effects may occur even after you have stopped treatment.
- If you have any further questions, ask your doctor.
- If you get any side effects talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Tysabri is and what it is used for

Tysabri is used to treat multiple sclerosis (MS). It contains the active substance natalizumab. This is called a monoclonal antibody.

MS causes inflammation in the brain that damages the nerve cells. This inflammation happens when white blood cells get into the brain and spinal cord. This medicine stops the white blood cells getting through to the brain. This reduces nerve damage caused by MS.

Symptoms of multiple sclerosis
The symptoms of MS vary from patient to patient, and you may experience some or none of them.

They may include: walking problems, numbness in the face, arms or legs; problems with vision; tiredness; feeling off-balance or light headed; bladder and bowel problems; difficulty in thinking and concentrating; depression; acute or chronic pain; sexual problems; 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).

How Tysabri can help
In trials, this medicine approximately halved the build-up of disability caused by MS, and decreased the number of MS attacks by about two-thirds. While you are treated with this medicine you might not notice any improvement, but it may still be working to prevent your MS becoming worse.

2. What you need to know before you receive Tysabri

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

You must not be given Tysabri

- If you are **allergic** to natalizumab or any of the other ingredients of this medicine (listed in section 6).
- If you have been **diagnosed with PML** (*progressive multifocal leukoencephalopathy*). PML is an uncommon infection of the brain.
- If your **immune system** has a serious problem. This may be due to disease (such as HIV), or to a medicine you are taking, or have taken in the past (see below).
- If you are taking **medicines that affect your immune system,** including certain other medicines used to treat MS. These medicines cannot be used with Tysabri.
- If you **have cancer** (unless it is a type of skin cancer called *basal cell carcinoma*).

Warnings and precautions

You need to discuss with your doctor whether Tysabri is the most suitable treatment for you. Do this before you start taking Tysabri, and when you have been receiving Tysabri for more than two years.

Possible brain infection (PML)

Some people receiving this medicine (fewer than 1 in 100) have had an uncommon brain infection called PML (*progressive multifocal leukoencephalopathy*). PML can lead to severe disability or death.

- Before starting treatment, **all patients will have blood tests** arranged by the doctor for JC virus infection. JC virus is a common virus that does not normally make you ill. However, PML is linked to an increase of JC virus in the brain. The reason for this increase in some patients treated with Tysabri is not clear. Before and during treatment, your doctor will test your blood to check if you have antibodies to the JC virus, which are a sign that you have been infected by the JC virus.
- Your doctor will arrange a **Magnetic Resonance Imaging (MRI) scan**, which will be repeated during treatment to rule out PML.
- **The symptoms of PML** may be similar to an MS relapse (see section 4, *Possible side effects*). You can also get PML up to 6 months after stopping Tysabri treatment.

  Tell your doctor as soon as possible if you notice your MS getting worse, if you notice any new symptoms while you are on Tysabri treatment or for up to 6 months afterwards.
- **Tell your partner or caregivers** about what to look out for (see also section 4, *Possible side effects*). Some symptoms might be difficult to spot by yourself, such as changes in mood or

behaviour, confusion, speech and communication difficulties. If you get any of these, **you may need further tests**. Keep looking out for symptoms in the 6 months after stopping Tysabri.

- Keep the patient alert card you have been given by your doctor. It includes this information. Show it to your partner or caregivers.

Three things can increase your risk of PML with Tysabri. If you have two or more of these risk factors, the risk is increased further:

- **If you have antibodies to the JC virus** in your blood. These are a sign that the virus is in your body. You will be tested before and during Tysabri treatment.

- **If you are treated for a long time** with Tysabri, especially if it is more than two years.

- **If you have taken a medicine called an *immunosuppressant***, that reduces the activity of your immune system.

Another condition, called JCV GCN (*JC virus granule cell neuronopathy*), is also caused by JC virus and has occurred in some patients receiving Tysabri. The symptoms of JCV GNC are similar to PML.

For those with a lower risk of PML, your doctor may repeat the test regularly to check that:

- You still do not have antibodies to the JC virus in your blood.

- If you have been treated for more than 2 years, you still have a lower level of JC virus antibodies in your blood.

If someone gets PML
PML can be treated, and Tysabri treatment will be stopped. However, some people get a reaction as Tysabri is removed from the body. This reaction (known as IRIS or immune reconstitution inflammatory syndrome) may lead to your condition getting worse, including worsening of brain function.

Look out for other infections
Some infections other than PML may also be serious and can be due to viruses, bacteria, and other causes.

Tell a doctor or nurse immediately if you think you have an infection (see also section 4, *Possible side effects*).

Changes in blood platelets
Natalizumab may reduce platelets in the blood which are responsible for clotting. This may result in a condition called thrombocytopenia (see section 4) in which your blood may not clot quickly enough to stop bleeding. This can lead to bruising as well as other more serious problems such as excessive bleeding. You should talk to your doctor immediately if you have unexplained bruising, red or purple spots on the skin (called petechiae), bleeding from skin cuts that does not stop or oozes, prolonged bleeding from the gums or nose, blood in urine or stools, or bleeding in the whites of your eyes.

Children and adolescents
Do not give this medicine to children or adolescents under the age of 18 years.

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

- You **must not** be given this medicine if you are now being treated with medicines that affect your **immune system**, including certain other medicines to treat your MS.

- You might not be able to use this medicine if you have **previously** had any medicines that affect your immune system.

Pregnancy and breast-feeding
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.

- **Do not use this medicine if you are pregnant,** unless you have discussed this with your doctor. Be sure to tell your doctor immediately if you get pregnant, think you may be pregnant, or if you are planning to become pregnant.

- **Do not breast-feed whilst using Tysabri.** Your doctor will help you decide whether you should choose to stop breast-feeding or stop using the medicine.

The risk to the baby and benefit to the mother will be taken into consideration by your doctor.

Driving and using machines
Dizziness is a very common side effect. If you are affected, do not drive or use machines.

Tysabri contains sodium
Each vial of this medicine contains 2.3 mmol (or 52 mg) of sodium. After dilution for use, this medicinal product contains 17.7 mmol (or 406 mg) sodium per dose. This should be considered if you are on a controlled sodium diet.

3. How Tysabri is given

Tysabri IV infusion will be given to you by a doctor experienced in the treatment of MS. Your doctor may switch you directly from another medicine for MS to Tysabri if there are no problems caused by your previous treatment.

- Your doctor will order **blood tests** for antibodies to the JC virus and other possible problems.

- Your doctor will arrange an **MRI scan**, which will be repeated during treatment.

- **To switch from some MS medicines,** your doctor may advise you to wait for a certain time to ensure that most of the previous medicine has left your body.

- For adults the recommended 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.

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

If you stop using Tysabri
Regular dosing with Tysabri is important, especially in the first few months of treatment. It is important to continue with your medicine for as long as you and your doctor decide that it is helping you. 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 restarting treatment.

Checking for allergic reactions
A few patients have had an allergic reaction to this medicine. Your doctor may check for allergic reactions during the infusion and for 1 hour afterwards. See also section 4, *Possible side effects*.

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.

Will Tysabri always work?
In a few patients receiving Tysabri, the body's natural defences may stop the medicine from working properly over time, as the body develops antibodies to the medicine. Your doctor can decide whether this medicine is not working properly for you from blood tests and will stop the treatment, if necessary.

If you have any further questions on Tysabri, ask your doctor. Always use this medicine exactly as described in this leaflet or as your doctor has told you. Check with your doctor if you are not sure.

4. Possible side effects

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

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

Signs of a brain infection
- Changes in personality and behaviour such as confusion, delirium or loss of consciousness,
- Seizures (fits)
- Headache
- Nausea / vomiting
- Stiff neck
- Extreme sensitivity to bright light
- Fever
- Rash (anywhere on the body)

These symptoms may be caused by an infection of the brain (*encephalitis or PML*) or its covering layer (*meningitis*).

Signs of other serious infections

- An unexplained fever
- Severe diarrhoea
- Shortness of breath
- Prolonged dizziness
- Headache
- Weight loss
- Listlessness
- Impaired vision
- Pain or redness of the eye(s)

Signs of an allergic reaction

- 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)

These are most likely during or shortly after the infusion.

Signs of a possible liver problem

- Yellowing of your skin or the whites of your eyes
- Unusual darkening of the urine
- Abnormal liver function test

Speak to a doctor or nurse immediately if you get any of the side effects listed above, or if you think you have an infection. **Show your patient alert card** and this package leaflet to any doctor or nurse who treats you, not only to your neurologist.

Other side effects

Very common (may affect more than 1 in 10 people)

- Urinary tract infection
- Sore throat and runny or blocked up nose
- Headache
- Dizziness
- Feeling sick (*nausea*)
- Joint pain
- Tiredness
- Dizziness, feeling sick (*nausea*), itching and chills during or shortly after infusion

Common (may affect up to 1 in 10 people)

- Anaemia (decrease in your red blood cells which can make your skin pale and can make you feel breathless or lacking energy)
- Allergy (*hypersensitivity*)

- Shivering
- Itchy rash (*hives*)
- Being sick (*vomiting*)
- Fever
- Difficulty breathing (*dyspnoea)*
- Reddening of the face or body (*flushing*)
- Herpes infections
- Discomfort around the place you have had your infusion. You could experience bruising, redness, pain, itching or swelling

Uncommon (may affect up to 1 in 100 people)
- Severe allergy (*anaphylactic reaction*)
- Progressive multifocal leukoencephalopathy (PML)
- Inflammatory disorder after discontinuation of the medicinal product
- Facial swelling
- An increase in the number of white blood cells (*eosinophilia*)
- Reduction in blood platelets
- Easy bruising (purpura)

Rare (may affect up to 1 in 1,000 people)
- Herpes infection in the eye
- Severe anaemia (decrease in your red blood cells which can make your skin pale and can make you feel breathless or lacking energy).
- Severe swelling under the skin
- High levels of bilirubin in the blood (*hyperbilirubinaemia*) which may cause symptoms such as yellowing of your eyes or skin, fever and tiredness

Not known (frequency cannot be estimated from the available data)
- Unusual infections (so-called "*opportunistic infections*")
- Damage to your liver

Speak to your doctor as soon as possible if you think you have an infection.
You will also find this information in the patient alert card you have been given by your doctor.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via
the Yellow Card Scheme.
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Tysabri

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

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

Unopened vial:
Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

Diluted solution:
After dilution, immediate use is recommended. If not used immediately, the diluted solution must be stored at 2˚C to 8˚C and infused within 24 hours of dilution.

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

6. Contents of the pack and other information

What Tysabri contains
The active substance is natalizumab. Each 15 mL vial of concentrate contains 300 mg natalizumab (20 mg per mL). When diluted, the solution for infusion contains approximately 2.6 mg per mL of natalizumab.

The other ingredients are:
Sodium phosphate, monobasic, monohydrate,
Sodium phosphate, dibasic, heptahydrate,
Sodium chloride (see section 2 'Tysabri contains sodium'),
Polysorbate 80 (E 433)
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.

Marketing Authorisation Holder
Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhoevedorp
The Netherlands

Manufacturer
Biogen Netherlands B.V.
Prins Mauritslaan 13
1171 LP Badhovedorp
The Nertherlands

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The following information is intended for 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 the medicine. 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 solution to mix completely. Do not shake.

4. Tysabri must not be mixed with other medicinal products or diluents.

5. Visually inspect the diluted medicinal product for particles or discolouration prior to administration. Do not use if it is discoloured or if foreign particles are seen.

6. The diluted medicinal product is to be used as soon as possible and within 24 hours of dilution. If the diluted medicinal product is stored at 2 to 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 per 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. In order to improve traceability of biological medicinal products, the product name (Tysabri) and batch number of the administered product should be clearly recorded.

11. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.