Package leaflet: Information for the patient

Tysabri 150 mg solution for injection in pre-filled syringe
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 this medicine, and when you have been receiving it 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 or 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 this medicine. The symptoms of JCV GCN 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
- **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 stop breast-feeding, or stop using the medicine.

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. 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
This medicine contains less than 1 mmol sodium (23 mg) per 300 mg dose, so it is essentially 'sodium-free'.

3. How Tysabri is given

Tysabri injections will be prescribed to you by a doctor experienced in the treatment of MS. Your doctor may switch you directly from another medicine to Tysabri if there are no signs of problems caused by your previous treatment. Tysabri injections will be given to you by a healthcare professional.

- 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.

- If your condition allows, your doctor may talk to you about receiving injections outside a clinic (e.g. at home).

- For adults the recommended dose is 300 mg, given once every 4 weeks.

- Each dose is given as **two injections** under the skin, in your thigh, stomach or back of your arm. This takes up to 30 minutes.

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

If you stop using Tysabri
Regular dosing with this medicine 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 injections 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.

Subcutaneous is abbreviated as SC on the syringe label.

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 injection.

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

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 been injected. You could experience pain, bruising, redness, 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 1000 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 of brain and eyes
- 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.

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.

Store in a refrigerator.
Do not freeze.
The syringes can be kept in their original packaging for up to 24 hours at room temperature (up to 25° C).
The syringes must not be returned to the refrigerator.
Keep the syringes in the outer carton in order to protect from light.

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

6. Contents of the pack and other information

What Tysabri contains
The active substance is natalizumab.
Each 1 mL pre-filled syringe contains 150 mg 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 colourless to slightly yellow, slightly opalescent to opalescent liquid.
Each carton contains two syringes.
Tysabri is available in packs containing 2 pre-filled syringes.

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

Manufacturer

FUJIFILM Diosynth Biotechnologies Denmark ApS
Biotek Allé 1

DK-3400 Hillerød
Denmark

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

This leaflet was last revised in November 2023.

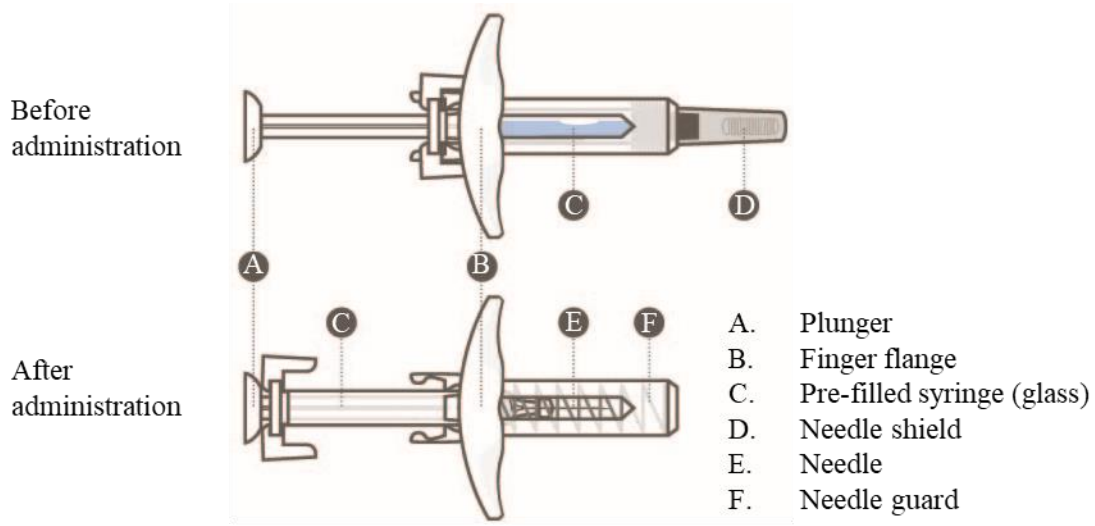
The following information is intended for healthcare professionals only:

Before administering Tysabri subcutaneous injection outside a clinical setting (OCS) e.g. at home, the OCS Administration Checklist must be completed for each patient, prior to each administration, to ensure that the injection can be administered.

The 300 mg recommended dose should be administered using two 150 mg pre-filled syringes, see section 3 below.

Instructions for administration

The pre-filled syringe has a needle guard system that will automatically activate when the plunger is fully depressed. As you let go of the plunger, the needle guard will cover the exposed needle.



1. Remove dose pack from the refrigerator and allow to warm to room temperature (up to 25ºC) before administering the injections. Recommended warm up time is 30 minutes.

Date and time of removal of the dose pack from the refrigerator must be recorded on the carton.

- **Do not use external heat sources** such as hot water to warm the pre-filled syringes.
- **Do not** touch or recap the needle at any stage. This is to avoid accidental needle stick injury.

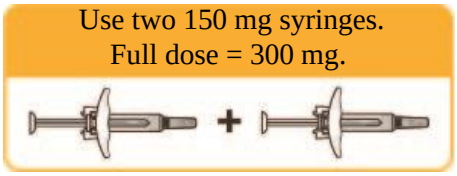
2. **Remove both product syringes** from the tray. Check that the medicinal product in each pre-filled syringe is a colourless to slightly yellow, slightly opalescent solution that is essentially free of visible particles. You might see air bubbles in the display windows. This is normal and will not affect the dose.

- **Check both** the pre-filled syringes. **Do not** use them if:
  - they are past the expiry date marked on the syringe label (EXP).

  or
  - have been stored at room temperature (up to 25ºC) for longer than 24 hours.
  - the colour and clarity of the liquid is not consistent with the above, or if the liquid contains floating particles.
  - there are any signs of damage (cracks, chips, etc.).

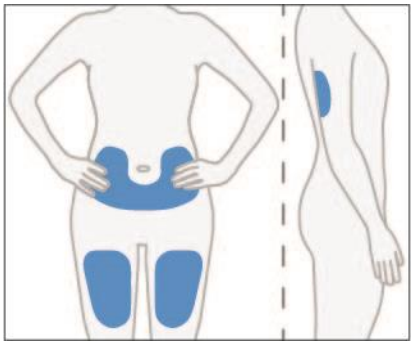
- If you notice any of the above, contact your pharmacy **immediately**.

3. A full dose is equivalent to two syringes administered consecutively and within 30 minutes of each other.



4. Use aseptic technique (clean and germ free) and a flat work surface during the injection procedure.

5. Choose the first subcutaneous injection site in the thigh, abdomen, or the back of the upper arm.

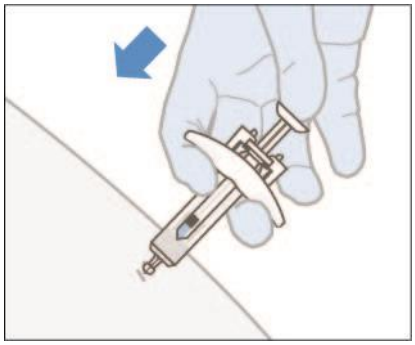


- **Do not** inject into an area of the body where the skin is irritated, reddened, bruised, infected, or scarred in any way.

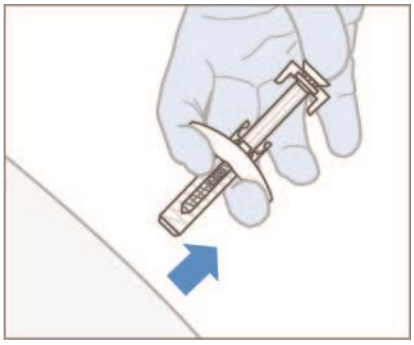
6. Give the first injection.
  - Choose an injection site and wipe the skin with an alcohol wipe.
  - Let the injection site dry on its own before injecting.
  - **Do not** touch or blow on this area again before giving the injection.
  - Remove the needle shield.

- Gently pinch the skin around the cleaned injection site using thumb and forefinger to create a slight bulge.
- Hold the pre-filled syringe at a 45°-90° angle to the injection site. Quickly insert the needle straight into the skin fold until the needle is fully under the skin.

7. Slowly push the plunger in one smooth motion until the syringe is completely empty. Do not pull back on the plunger.



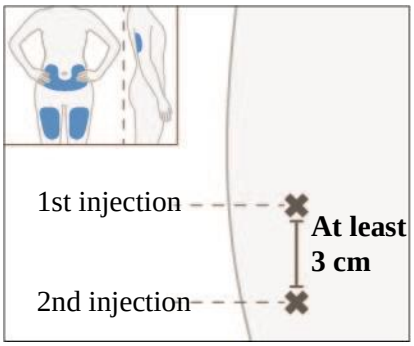
8. Before removing the syringe, check that the syringe is empty. If you see any blood, press a cotton ball or gauze on the site. Do not rub the skin after the injection.When removing the syringe from the injection site, let go of the plunger WHILE pulling the needle straight out. As you let go of the plunger, the needle guard will cover the exposed needle.



9. Administer injections one after the other without significant delay. In the event that the second injection cannot be administered immediately following the first injection, the second injection should be administered no later than 30 minutes after the first injection. The second injection should be at least 3 cm away from the first injection location.

Patients should be **observed during the subcutaneous injections and for 1 hour after** for signs and symptoms of injection reactions including hypersensitivity. **After the first 6 Tysabri doses**, regardless of route of administration, patients should be observed after subcutaneous injection according to clinical judgement.

Promptly discontinue injection upon the first observation of any signs or symptoms consistent with an allergic reaction [see SmPC section 4.4].



10. Dispose of the used syringe in accordance with local requirements.