Package leaflet: Information for the user

Tegsedi 284 mg solution for injection in pre-filled syringe
inotersen

Read all of this leaflet carefully before you start using 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, pharmacist or nurse.
- 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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Tegsedi is and what it is used for

Tegsedi contains the active substance inotersen. Inotersen is used to treat adults with hereditary transthyretin amyloidosis. Hereditary transthyretin amyloidosis is a genetic disease, which causes build-up of small fibres of a protein called transthyretin in the organs of your body stopping them from working properly. Tegsedi is used when the disease is causing symptoms of polyneuropathy (nerve damage).

Inotersen, is a type of medicine called an antisense oligonucleotide inhibitor. It works by reducing production of transthyretin by the liver and so lowers the risk of fibres of transthyretin being deposited in body organs and causing symptoms.

2. What you need to know before you use Tegsedi

Do not use Tegsedi if:
- You are allergic to inotersen or any of the other ingredients of this medicine (listed in section 6).
- Tests show you have excessively low numbers of platelets, the cells in your blood which stick together helping it clot
- Tests of kidney function or protein in the urine show signs of severe kidney problems
- You have severe reduction in liver function (hepatic impairment)

Warnings and precautions

Before you begin treatment with Tegsedi, your doctor will measure your blood cells, liver function, kidney function, vitamin A and protein levels in your urine. You may also be tested to assure a negative pregnancy result. Unless explicitly advised by your doctor, you will only be treated with Tegsedi if these results are all at acceptable levels and your pregnancy result is negative. Your doctor will repeat these checks regularly during treatment. It is important that you have these regular blood and urine tests for as long as you are taking Tegsedi.

Thrombocytopenia
Tegsedi may reduce cells in the blood responsible for clotting of the blood (platelets), which may result in a condition called thrombocytopenia at any time during treatment with Tegsedi (see section 4). When you do not have enough platelets, like in thrombocytopenia, 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 and internal bleeding. Your doctor will check your blood for levels of platelets before treatment and regularly during the entire course of treatment with Tegsedi. It is important that you have these regular blood tests for as long as you are taking Tegsedi because of the risk of serious bleeding caused by low platelet counts. If you stop taking Tegsedi, your blood levels should be checked 8 weeks after discontinuation.

You should see your doctor immediately if you have unexplained bruising or a rash of small patches of red appearing on the skin (called petechiae), bleeding from skin cuts that does not stop or oozes, bleeding from the gums or nose, blood in urine or stools, bleeding in the whites of your eyes. Call for immediate help if you have stiffness of the neck or an unusual and severe headache because these symptoms may be caused by bleeding in the brain.

Glomerulonephritis / kidney problems

Glomerulonephritis is a condition of your kidneys, where they do not work properly due to inflammation and kidney damage. Some patients treated with inotersen have developed this condition. Symptoms of glomerulonephritis are foaming urine, pink or brown coloured urine, blood in the urine, and passing less urine than usual.

Some patients treated with inotersen have also developed a decline in their kidney function without having had glomerulonephritis.

Your doctor will check your kidney function before treatment and regularly during treatment with Tegsedi. It is important that you have these regular blood tests for as long as you are taking Tegsedi because of the risk of kidney problems. If you stop taking Tegsedi then your kidney function should be checked 8 weeks after discontinuation. If you develop glomerulonephritis, your doctor will treat you for this condition.

Vitamin A deficiency

Tegsedi can lower your body's levels of vitamin A (also called retinol). Your doctor will measure these, and if they are already low, this should be corrected and any symptoms resolved before you start treatment with Tegsedi. Symptoms of low vitamin A include:

- Dry eyes, poor vision, decrease in night vision, hazy or cloudy vision

If you have problems with your sight or any other eye problems when you are using Tegsedi, you should speak to your doctor. Your doctor may refer you to an eye specialist for a check-up if it is necessary.

Your doctor will ask you to take a daily vitamin A supplement during treatment with Tegsedi.

Both excess and deficient levels of vitamin A can harm the development of your unborn child. Therefore, women of child-bearing age should exclude any pregnancy, before treatment initiation with Tegsedi and should practise effective contraception (see section *"Pregnancy and breast-feeding"* below).

If you are planning to become pregnant you should stop taking inotersen including vitamin A supplementation and ensure that your vitamin A levels have returned to normal before conception is attempted.

If you have an unplanned pregnancy you should stop taking inotersen. Due to the prolonged activity of Tegsedi, however, your reduced vitamin A levels may persist. It is unknown if continuation of your vitamin A supplementation with 3 000 IU per day will be harmful to your unborn child in the first trimester of your pregnancy, but this dose should not be exceeded. You should resume the vitamin A supplementation during your second and third trimesters of your pregnancy if your vitamin A levels have not yet returned to normal, because of the increased risk of vitamin A deficiency in the third trimester.

Liver injury and monitoring

Tegsedi may cause serious liver problems. You will need a blood test before you start taking inotersen to check whether your liver is working properly. You will also need these blood tests regularly while you are taking this medicine. It is important that you have these regular blood tests for as long as you are taking Tegsedi.

Liver transplant rejection

Talk to your doctor before using Tegsedi if you have previously received a liver transplant. Cases of liver transplant rejection have been reported in patients being treated with Tegsedi. Your doctor will monitor you regularly for this during treatment with Tegsedi.

Children and adolescents
Tegsedi should not be used in children and adolescents under 18 years old.

Other medicines and Tegsedi
Tell your doctor or pharmacist if you are taking, have recently taken or might use any other medicines. It is important that you tell your doctor if you are already being treated with any of the following:
- Medicines to prevent blood clots or that lower the platelet numbers in your blood, e.g., acetylsalicylic acid, heparin, warfarin, clopidogrel, rivoraxaban and dabigatran.
- Any medicines that may alter your kidney function or may damage the kidneys, e.g., sulfonamides (used as an antibacterial), anilides (used to treat fever, aches and pains), aldosterone antagonists (used as a diuretic) and natural opium alkaloids and other opioids (used for treatment of pain).

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 using this medicine.

Women of child-bearing age

Tegsedi will reduce the level of vitamin A in your body, which is important for normal foetal development during pregnancy. It is unknown if vitamin A supplementation can compensate for the risk of vitamin A deficiency that might affect your unborn child (see *"Warnings and precautions"* above). If you are a woman of child-bearing age, you should practise effective contraception and any pregnancy should be excluded before starting the treatment with Tegsedi.

Pregnancy

You should not use Tegsedi if you are pregnant, unless explicitly advised by your doctor.

Breast-feeding

Inotersen may pass into breast milk. A risk to the breastfed infant cannot be excluded. You should consult your doctor if you should either stop breast-feeding or stop the treatment with Tegsedi.

Driving and using machines

Use of Tegsedi has not been shown to affect ability to drive or use machinery.

Tegsedi contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per 1.5 mL, that is to say essentially 'sodium free'

3. How to use Tegsedi

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose of Tegsedi is one dose of 284 mg inotersen.

Doses should be administered once every week. All subsequent doses should be injected once weekly on the same day each week.

Route and method of administration

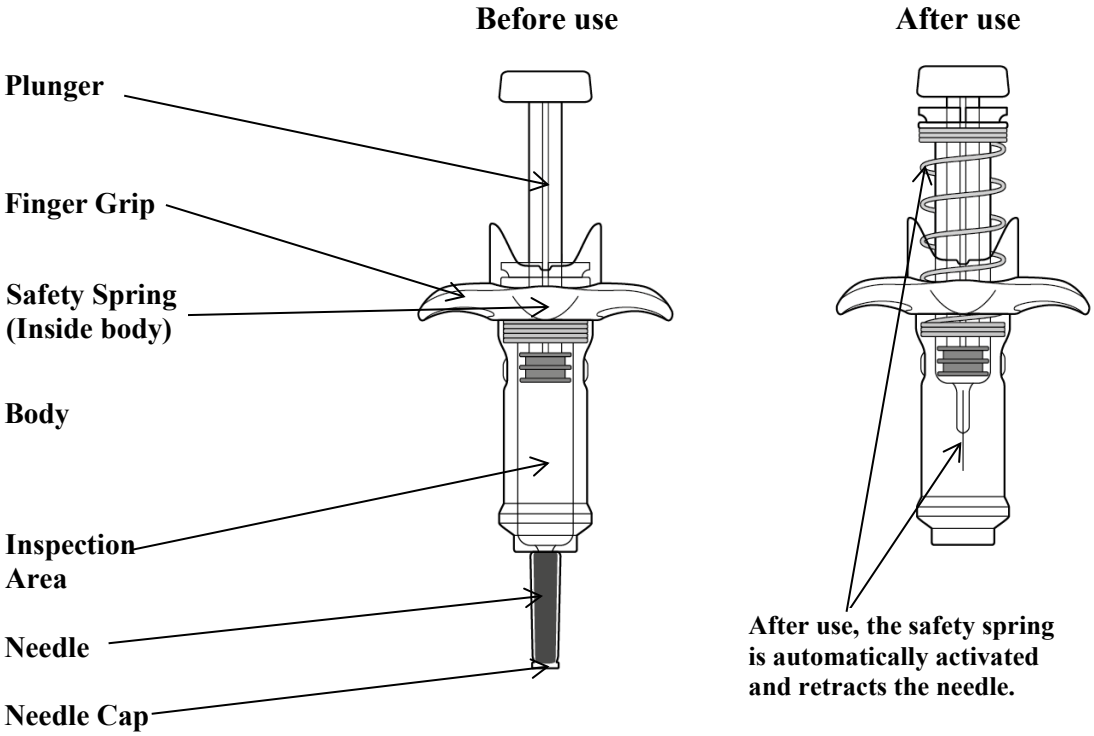
Tegsedi is for injection under the skin (subcutaneous use) only.

Instructions for use

Before using your pre-filled syringe, your doctor should show you or your caregiver how to use it the right way. If you or your caregiver have any questions, ask your doctor.

Read the instructions for use before you start using your pre-filled syringe and each time you get a repeat prescription. There may be new information.

Guide to parts



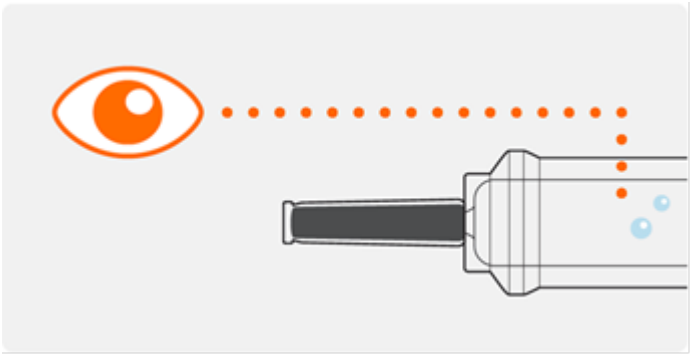
Each pre-filled syringe contains one dose and is for one-time use only**.**

WARNINGS
Do not remove needle cap until you have reached **Step 6** of these instructions and are ready to inject Tegsedi; **Do not** share your syringe with another person or re-use your syringe; **Do not** use if the pre-filled syringe is dropped onto a hard surface or is damaged; **Do not** freeze the pre-filled syringe; If any of the above happens, throw away the pre-filled syringe in a puncture-resistant (sharps) container and use a new pre-filled syringe.
PREPARATION
1. Gather supplies
- 1 Pre-filled syringe from the refrigerator - 1 Alcohol wipe (not supplied) - 1 Gauze pad or cotton ball (not supplied) - 1 Puncture-resistant (sharps) container (not supplied) **Do not** inject the medicine until you have gathered the supplies listed.
2. Prepare to use your pre-filled syringe

- Remove the plastic tray from the carton and check the expiry date. Do not use if the expiry date has passed.
- Let the pre-filled syringe reach room temperature (20 °C to 25 °C) for 30 minutes before injecting it. **Do not** warm the pre-filled syringe in any other way. For example, **do not** warm in a microwave or hot water, or near other heat sources.
- Remove the pre-filled syringe from the tray by holding onto the syringe body.

Do not move the plunger.

3. Check medicine in the pre-filled syringe

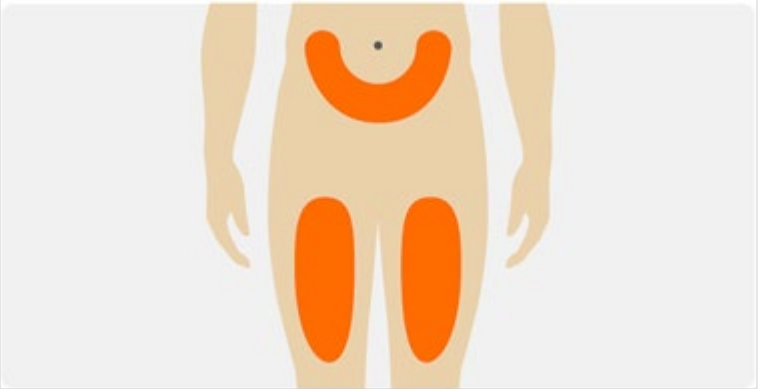


Look in the inspection area to check that the solution is clear and colourless or pale yellow. It is normal to see air bubbles in the solution. You do not need to do anything about it.

Do not use if the solution looks cloudy, discoloured, or has particles.

If the solution looks cloudy, discoloured or has particles, throw the pre-filled syringe away in a puncture resistant (sharps) container, and use a new pre-filled syringe.

4. Choose the injection site



Choose an injection site on your abdomen (belly) or the front of your thigh.

The injection site may also be on the outer area of the upper arm if Tegsedi is administered by a caregiver.

Do not inject into the 3cm area around the belly-button (navel).

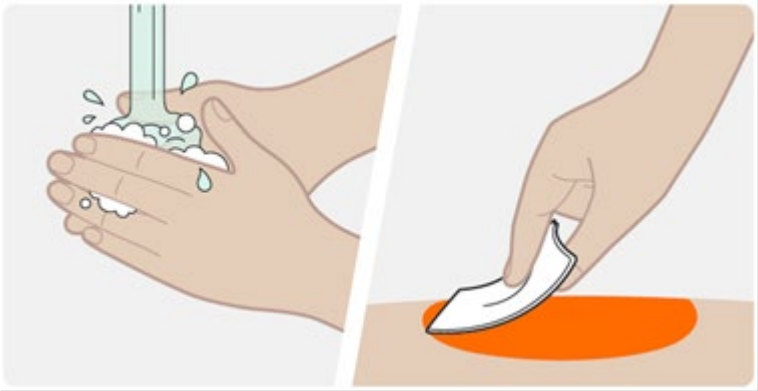
Do not inject into the same site each time.

Do not inject where skin is bruised, tender, red or hard.

Do not inject into tattoos, scars or damaged skin.

Do not inject through clothing.

5. Clean the injection site



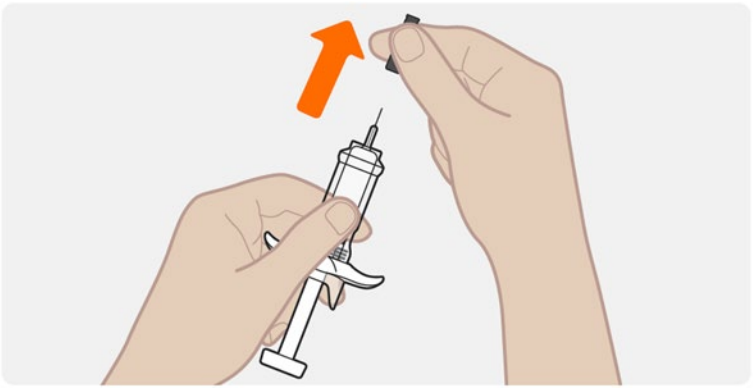
Wash your hands with soap and water.

Clean the injection site with an alcohol wipe in a circular motion. Let the skin air dry.

Do not touch the area again before injecting.

INJECTION

6. Remove the needle cap



Hold the pre-filled syringe by the body, with the needle facing away from you.

Remove needle cap by pulling it straight off. Do not twist it off.

You may see a drop of liquid at the end of the needle. This is normal.

Keep your hands away from the plunger to avoid pushing the plunger before you are ready to inject.

Do not remove the needle cap until right before you inject.

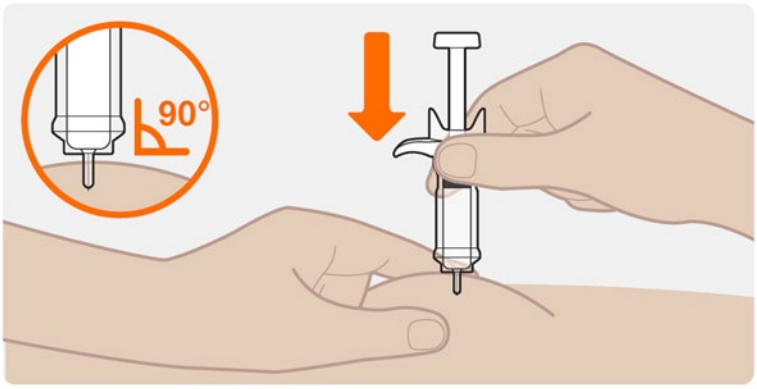
Do not pull the cap off while holding the pre-filled syringe by the plunger. Always hold by the body of the syringe.

Do not let the needle touch any surface.

Do not remove any air bubbles from the pre-filled syringe.

Do not put the needle cap back onto the pre-filled syringe.

7. Insert the needle



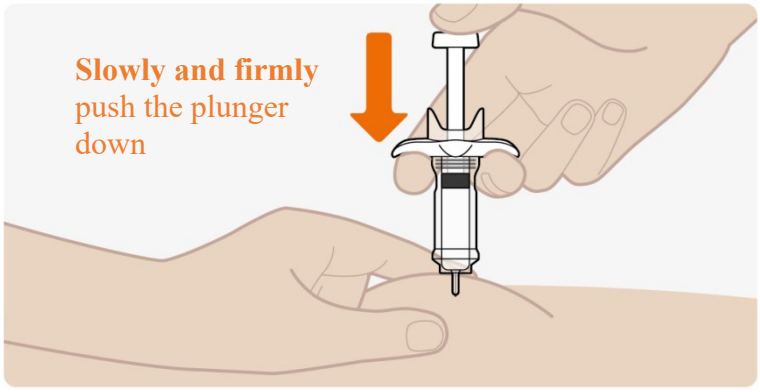
Hold the pre-filled syringe in 1 hand.

Hold the skin around at the injection site as your healthcare provider has instructed you. You should either gently pinch the skin at the injection site or give the injection without pinching the skin.

Slowly insert the needle into the chosen injection site at a 90° angle until it is fully inserted.

Do not hold the pre-filled syringe by the plunger or push against the plunger to insert the needle.

8. Start the injection



Slowly and firmly push the plunger all the way down until the medicine is injected. Make sure the needle stays fully inserted in the injection site while you are injecting the medicine.

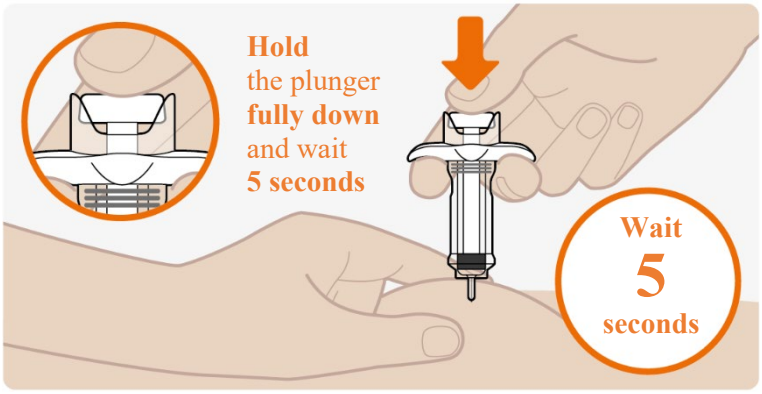
It is important to push the plunger all the way down.

Your pre-filled syringe may make a click sound as you push the plunger down. This is normal. This **does not** mean that the injection is finished.

The plunger can feel stiff towards the end of the injection. You may need to press a little harder on the plunger to make sure you have pushed it as far as it will go.

Do not let go of the plunger.

9. Push the plunger down

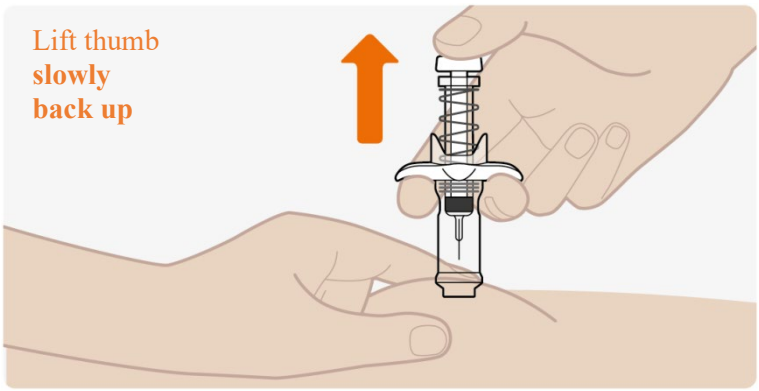


Push firmly on the plunger at the end of the injection. Hold the plunger fully down and wait for **5 seconds**. If you let go of the plunger too quickly, you may lose some of the medicine.

The plunger will start to lift automatically which means that the plunger has been pushed fully down.

Press down again if the plunger does not start to lift automatically.

10. Complete the injection



Slowly lift up on the plunger and let the safety spring push the plunger up automatically.

The needle should now be retracted safely inside the pre-filled syringe, and the safety mechanism spring visible on the outside of the plunger.

When the plunger comes to a stop, your injection is complete.

If the plunger does not rise up automatically when you release the pressure, it means the safety spring did not activate and you should push the plunger again but harder.

Do not pull the plunger up by hand. Lift the whole pre-filled syringe straight up.

Do not try to replace the cap on the retracted needle.

Do not rub the injection site.

DISPOSAL AND CARE

Dispose of the used pre-filled syringe

Put the used pre-filled syringe in a sharps disposal container right away after use. Do not throw away the pre-filled syringe in your household waste.

If you use more Tegsedi than you should
Contact your doctor or pharmacist, or go to a hospital emergency department immediately, even if you have no symptoms.

If you forget to use Tegsedi
If you miss your dose of Tegsedi, then you should have your next dose as soon as possible, unless the next scheduled dose is within two days, in which case the missed dose should be skipped and the next dose given at the scheduled time.

Do not take a double dose to make up for a forgotten dose.

If you stop using Tegsedi
Do not stop using Tegsedi unless your doctor tells you to.

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

4. Possible side effects

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

Serious side effects
If you get any of the following side effects, stop using Tegsedi and contact your doctor immediately:
- Symptoms that could indicate glomerulonephritis, (where your kidneys do not work properly), such as foaming urine, pink or brown coloured urine, blood in the urine, or passing less urine than usual. Glomerulonephritis is a common side effect of inotersen (may affect up to 1 in 10 people).
- Symptoms that could indicate thrombocytopenia (where blood will not clot due to low levels of blood platelets), such as unexplained bruising or a rash of small patches of red appearing on the skin (called petechiae), bleeding from skin cuts that does not stop or oozes, bleeding from the gums or nose, blood in urine or stools, or bleeding in the whites of your eyes. A low level of blood platelets is a very common side effect of inotersen (may affect more than 1 in 10 people).
- Symptoms that could indicate liver injury, such as yellowing of the eyes or skin, or dark urine, potentially accompanied by itching of the skin, pain on the upper right side of your stomach area (abdomen), loss of appetite, bleeding or bruising more easily than normal, or feeling tired.

Call for immediate help if you have stiffness of the neck or an unusual and severe headache because these symptoms may be caused by bleeding in the brain.

Other side effects
Very common (may affect more than 1 in 10 people)
- Reduction in red blood cells which can make the skin pale and cause weakness or breathlessness (anaemia)
- Headache
- Vomiting, or nausea (feeling sick)
- Increase in body temperature
- Feeling cold (chills) or shivering
- Injection site pain, redness, itching or bruising
- Swelling of the ankles, feet or fingers (peripheral oedema)

Common (may affect up to 1 in 10 people)
- An increase in the number of white blood cells called eosinophils in your blood (eosinophilia)
- Decreased appetite
- Feeling faint or dizzy, especially on standing up (low blood pressure, hypotension)
- Bruising
- Collection of blood within the tissues, that may look similar to severe bruising (haematoma)
- Itching
- Rash
- Kidney damage leading to poor kidney function or kidney failure
- Changes to your blood and urine test results (this may indicate liver or kidney damage)
- Flu like symptoms, such as high temperature, aches and chills (influenza-like illness)

- Injection site swelling or skin discolouration

Uncommon (may affect up to 1 in 100 people)
- Allergic reaction

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 via the national reporting system:

United Kingdom
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 Tegsedi

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, tray and on the pre-filled syringe after "EXP". The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Tegsedi may be stored unrefrigerated for up to 6 weeks at a temperature below 30°C. If unrefrigerated and not used within 6 weeks then this medicine should be discarded.
Store in the original package in order to protect from light.

Do not use this medicine if you notice that the contents are cloudy or contains particles.

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 Tegsedi contains
- The active substance is inotersen.
- Each ml contains 189 mg inotersen (as inotersen sodium). Each pre-filled syringe contains 284mg inotersen (as inotersen sodium) in 1.5 mL of solution.
- The other ingredients are water for injections, sodium hydroxide, and hydrochloric acid (see "Tegsedi contains sodium" in section 2).

What Tegsedi looks like and contents of the pack

Tegsedi is a clear, colourless to pale yellow solution for injection in a pre-filled syringe (injection).
Tegsedi is available in pack sizes of either 1 or 4 pre-filled syringes.
Not all pack sizes may be marketed.

Marketing Authorisation Holder

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Manufacturer

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