Package leaflet: Information for the user

Nplate 125 micrograms powder for solution for injection
Nplate 250 micrograms powder for solution for injection
Nplate 500 micrograms powder for solution for injection
Romiplostim

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 Nplate is and what it is used for

Nplate's active ingredient is romiplostim, which is a protein used to treat low platelet counts in patients with immune primary thrombocytopenia (called ITP). ITP is a disease in which your body's immune system destroys its own platelets. Platelets are the cells in your blood that help seal cuts and form blood clots. Very low platelet counts can cause bruising and serious bleeding.

Nplate is used to treat adult patients with ITP who may or may not have had their spleen removed and who have been previously treated with corticosteroids or immunoglobulins, where these treatments don't work. Nplate is also used to treat children aged 1 year and over with chronic ITP who may or may not have had their spleen removed and who have been previously treated with corticosteroids or immunoglobulins, where these treatments don't work.

Nplate works by stimulating the bone marrow (part of the bone which makes blood cells) to produce more platelets. This should help to prevent bruising and bleeding associated with ITP.

2. What you need to know before you use Nplate

Do not use Nplate:

- if you are allergic to romiplostim or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to other medicines that are produced by DNA technology using the micro-organism *Escherichia coli* (*E. coli*).

Warnings and precautions

- If you stop taking Nplate a low blood platelet count (thrombocytopenia) is likely to reoccur. If you stop taking Nplate your platelet count will have to be monitored, and your doctor will discuss appropriate precautions with you.

- If you are at risk of blood clots or if blood clots are common in your family. The risk of blood clotting may also be increased if you:
  - have liver problems;
  - are elderly (≥ 65 years);
  - are bedridden;
  - have cancer;
  - are taking the contraceptive pill or hormone replacement therapy;
  - have recently had surgery or suffered an injury;
  - are obese (overweight);
  - are a smoker.

Talk to your doctor, pharmacist or nurse before using Nplate.

If you have very high blood platelet counts this may increase the risk of blood clotting. Your doctor will adjust your dose of Nplate to ensure that your platelet count does not become too high.

Bone marrow changes (increased reticulin and possible bone marrow fibrosis)

Long-term use of Nplate may cause changes in your bone marrow. These changes may lead to abnormal blood cells or your body making less blood cells. The mild form of these bone marrow changes is called "increased reticulin" and has been observed in Nplate clinical trials. It is not known if this may progress to a more severe form called "fibrosis." Signs of bone marrow changes may show up as abnormalities in your blood tests. Your doctor will decide if abnormal blood tests mean that you should have bone marrow tests or if you should stop taking Nplate.

Worsening of blood cancers

Your doctor may decide to take a bone marrow biopsy if they decide it is necessary to ensure that you have ITP, and not another condition such as Myelodysplastic Syndrome (MDS). If you have MDS and receive Nplate you may have an increase in your blast cell counts and your MDS condition may worsen to become an acute myeloid leukaemia, which is a type of cancer of the blood.

Loss of response to romiplostim

If you experience a loss of response or failure to maintain a platelet response with romiplostim treatment, your doctor will investigate the reasons why including whether you are experiencing increased bone marrow fibres (reticulin) or have developed antibodies which neutralise romiplostim's activity.

Children and adolescents

Nplate is not recommended for use in children aged under 1 year.

Other medicines and Nplate

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

If you are also taking medicines which prevent blood clots (anticoagulants or antiplatelet therapy) there is a greater risk of bleeding. Your doctor will discuss this with you.

If you are taking corticosteroids, danazol, and/or azathioprine, which you may be receiving to treat your ITP, these may be reduced or stopped when given together with Nplate.

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 or pharmacist for advice before taking this medicine. Nplate is not recommended for use if you are pregnant unless indicated by your doctor.

It is not known whether romiplostim is present in human milk. Nplate is not recommended for use if you are breast-feeding. A decision on whether to discontinue breast-feeding or discontinue therapy with romiplostim should be made taking into account the benefit of breast-feeding to your child and the benefit of romiplostim therapy to you.

Driving and using machines

You should speak with your doctor before driving or using machines, as some side effects (e.g. temporary bouts of dizziness) may impair your ability to do so safely.

3. How to use Nplate

Adult and children (1 to 17 years):

Nplate will be given under the direct supervision of your doctor, who will closely control the amount of Nplate given to you.

Nplate is administered once a week as an injection under the skin (subcutaneous).

Your initial dose is 1 microgram of Nplate per kilogram of your body weight once a week. Your doctor will tell you how much you must take. Nplate should be injected once per week in order to keep your platelet counts up. Your doctor will take regular blood samples to measure how your platelets are responding and may adjust your dose as necessary.

Once your platelet count is under control, your doctor will continue to regularly check your blood. Your dose may be adjusted further in order to maintain long-term control of your platelet count.

Children (1 to 17 years old): in addition to adjusting your dose based on platelet counts, your doctor will also regularly reassess your body weight in order to adjust your dose.

If you use more Nplate than you should

Your doctor will ensure that you receive the right amount of Nplate. If you have been given more Nplate than you should, you may not experience any physical symptoms but your blood platelet counts may rise to very high levels and this may increase the risk of blood clotting. Therefore if your doctor suspects that you have been given more Nplate than you should, it is recommended that you are monitored for any signs or symptoms of side effects and that you are given appropriate treatment immediately.

If you use less Nplate than you should

Your doctor will ensure that you receive the right amount of Nplate. If you have been given less Nplate than you should, you may not experience any physical symptoms but your blood platelet counts may become low and this may increase the risk of bleeding. Therefore if your doctor suspects that you have been given less Nplate than you should, it is recommended that you are monitored for any signs or symptoms of side effects and that you are given appropriate treatment immediately.

If you forget to use Nplate

If you have missed a dose of Nplate, your doctor will discuss with you when you should have your next dose.

If you stop using Nplate

If you stop using Nplate, your low blood platelet count (thrombocytopenia) is likely to reoccur. Your doctor will decide if you should stop using Nplate.

4. Possible side effects

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

Possible side effects in adults with ITP

Very common: may affect more than 1 in 10 people
- headache;
- allergic reaction;
- upper respiratory tract infection.

Common: may affect up to 1 in 10 people
- bone marrow disorder, including increased bone marrow fibres (reticulin);
- trouble sleeping (insomnia);
- dizziness;
- tingling or numbness of the hands or feet (paraesthesia);
- migraine;
- redness of the skin (flushing);
- blood clot in a lung artery (pulmonary embolism);
- nausea;
- diarrhoea;
- abdominal pain;
- indigestion (dyspepsia);
- constipation;
- itching of the skin (pruritis);
- bleeding under the skin (ecchymosis);
- bruising (contusion);
- rash;
- joint pain (arthralgia);
- muscles pain or weakness (myalgia);
- pain in your hands and feet;
- muscle spasm;
- back pain;
- bone pain;
- tiredness (fatigue);
- injection site reactions;
- swelling in the hands and feet (oedema peripheral);
- flu like symptoms (influenza like illness);
- pain;
- weakness (asthenia);
- fever (pyrexia);
- chills;
- contusion;

- swelling of the face, lips, mouth, tongue or throat which may cause difficulty in swallowing or breathing (angioedema);
- gastroenteritis;
- palpitations;
- inflammation of the sinuses (sinusitis);
- inflammation of the passages that carry air to the lungs (bronchitis).

Common: may affect up to 1 in 10 people (may show up in blood or urine tests)
- low blood platelet count (thrombocytopenia) and low blood platelet count (thrombocytopenia) after stopping Nplate;
- higher than normal platelet counts (thrombocytosis);
- anaemia.

Uncommon: may affect up to 1 in 100 people
- bone marrow failure; disorder of the bone marrow that causes scarring (myelofibrosis); enlarged spleen (splenomegaly); bleeding of the vagina (vaginal haemorrhage), bleeding in the rectum (rectal haemorrhage); bleeding mouth (mouth haemorrhage); injection site bleeding (injection site haemorrhage);
- heart attack (myocardial infarction); increased heart rate;
- dizziness or a spinning sensation (vertigo);
- problems with the eyes including: bleeding in the eye (conjunctival haemorrhage); difficulty focussing or blurred vision (accommodation disorder, papilloedema or eye disorder); blindness; itchy eye (eye pruritus); increased tears (lacrimation increased); or visual disturbances;
- problems with the digestive system including: vomiting; bad breath (breath odour); difficulty swallowing (dysphagia); indigestion or heartburn (gastro-oesophageal reflux disease); blood in the stools (haematochezia); stomach discomfort; mouth ulcers or mouth blistering (stomatitis); discoloured teeth (tooth discolouration);
- weight decreased; weight increased; intolerance of alcohol; loss of appetite (anorexia or decreased appetite); dehydration;
- generally feeling unwell (malaise); chest pain; irritability; swelling of the face (face oedema); feeling hot; increased body temperature; feeling jittery;
- influenza; localised infection; inflammation of the passages in the nose and throat (nasopharyngitis);
- problems with the nose and throat including: cough; runny nose (rhinorrhoea); dry throat; shortness of breath or difficulty breathing (dyspnoea); nasal congestion; painful breathing (painful respiration)
- painful swollen joints caused by uric acid (food breakdown product) (gout);
- muscle tightness; muscular weakness; shoulder pain; muscle twitching;
- problems with your nervous system including involuntary muscle contractions (clonus); distorted sense of taste (dysgeusia); decrease in sense of taste (hypogeusia); decreased feeling of sensitivity, especially in the skin (hypoaesthesia); alteration in the nerve functions in the arms and legs (neuropathy peripheral); blood clot in the transverse sinus (transverse sinus thrombosis);
- depression; abnormal dreams;
- hair loss (alopecia); sensitivity to light (photosensitivity reaction); acne; allergic reaction in the skin upon contact with allergen (dermatitis contact); skin manifestation with rash and blisters (eczema); dry skin; redness of the skin (erythema); severe flaking or peeling rash (exfoliative rash); abnormal hair growth; thickening and itching of the skin due to repeated scratching (prurigo); bleeding beneath the surface of the skin or bruising under the skin (purpura); bumpy skin rash (rash papular); itchy skin rash (rash pruritic); generalised itchy rash (urticaria); bump on the skin (skin nodule); abnormal smell to the skin (skin odour abnormal);

- problems with the circulation including blood clot in the vein in the liver (portal vein thrombosis); deep vein thrombosis; low blood pressure (hypotension); increased blood pressure; blocking of a blood vessel or (peripheral embolism); reduced blood flow in the hands, ankles or feet (peripheral ischaemia); swelling and clotting in a vein, which may be extremely tender when touched (phlebitis or thrombophlebitis superficial); blood clot (thrombosis);
- a rare disorder characterised by periods of burning pain, redness and warmth in the feet and hands (erythromelalgia).

Uncommon: may affect up to 1 in 100 people (may show up in blood or urine tests)
- a rare type of anaemia in which the red blood cells, white blood cells and platelets are all reduced in number (aplastic anaemia);
- raised white blood cell count (leucocytosis);
- excess platelet production (thrombocythaemia); increased platelet counts; abnormal count in the cells in the blood that prevents bleeding (platelet count abnormal);
- changes in some blood tests (increase in transaminase; blood lactate dehydrogenase increased);
- or cancer of white blood cells (multiple myeloma);
- protein in the urine.

Possible side effects in children with ITP

Very common: may affect more than 1 in 10 people
- upper respiratory tract infection;
- pain in the mouth and throat (oropharyngeal pain);
- itchy, runny or blocked nose (rhinitis);
- cough;
- upper abdominal pain;
- diarrhoea;
- rash;
- fever (pyrexia);
- bruising (contusion).

Common: may affect up to 1 in 10 people
- gastroenteritis;
- sore throat and discomfort when swallowing (pharyngitis);
- inflammation of the eye (conjunctivitis);
- ear infection;
- inflammation of the sinuses (sinusitis);
- swelling in the limbs/hands/feet;
- bleeding beneath the surface of the skin or bruising under the skin (purpura);
- itchy rash (urticaria).

Uncommon: may affect up to 1 in 100 people
- higher than normal platelet counts (thrombocytosis).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly (see details below). By reporting side effects you can help provide more information on the safety of this medicine.

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 Nplate

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 and vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C – 8°C).
Do not freeze.
Store in the original carton in order to protect from light.

This medicine may be removed from the refrigerator for a period of 30 days at room temperature (up to 25°C) when stored in the original carton.

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 Nplate contains

- The active substance is romiplostim.

  Each vial of Nplate 125 micrograms powder for solution for injection contains a total of 230 micrograms of romiplostim. An additional overfill is included in each vial to ensure that 125 micrograms of romiplostim can be delivered. After dissolving, a deliverable amount of 0.25 mL solution contains 125 micrograms of romiplostim (500 micrograms/mL).

  Each vial of Nplate 250 micrograms powder for solution for injection contains a total of 375 micrograms of romiplostim. An additional overfill is included in each vial to ensure that 250 micrograms of romiplostim can be delivered. After dissolving, a deliverable amount of 0.5 mL solution contains 250 micrograms of romiplostim (500 micrograms/mL).

  Each vial of Nplate 500 micrograms powder for solution for injection contains a total of 625 micrograms of romiplostim. An additional overfill is included in each vial to ensure that 500 micrograms of romiplostim can be delivered. After dissolving, a deliverable amount of 1 mL solution contains 500 micrograms of romiplostim (500 micrograms/mL).

- The other ingredients are mannitol (E421), sucrose, L-histidine, hydrochloric acid (for pH adjustment) and polysorbate 20.

What Nplate looks like and contents of the pack

Nplate is a white powder for solution for injection supplied in a single-dose glass vial.

Carton containing 1 or 4 vials of either 125 micrograms (beige cap), 250 micrograms (red cap) or 500 micrograms of romiplostim (blue cap).

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Amgen Limited
216 Cambridge Science Park
Milton Road
Cambridge
CB4 0WA

United Kingdom

Manufacturer
Amgen Europe B.V.
Minervum 7061
4817 ZK Breda
The Netherlands

Manufacturer
Amgen Technology (Ireland) Unlimited Company
Pottery Road
Dun Laoghaire
Co Dublin
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

Amgen Limited
Tel: +44 (0)1223 420305

This leaflet was last revised in October 2021.

The following information is intended for healthcare professionals only:

Reconstitution:

Nplate is a sterile but unpreserved product and is intended for single use only. Nplate should be reconstituted in accordance with good aseptic practice.

- **Nplate 125 micrograms powder for solution for injection** should be reconstituted with 0.44 mL sterile water for injections, yielding a deliverable volume of 0.25 mL. An additional over fill is included in each vial to ensure that 125 mcg of romiplostim can be delivered (see vial content table below).

or

- **Nplate 250 micrograms powder for solution for injection** should be reconstituted with 0.72 mL sterile water for injections, yielding a deliverable volume of 0.5 mL. An additional overfill is included in each vial to ensure that 250 mcg of romiplostim can be delivered (see vial content table below).

or

- **Nplate 500 micrograms powder for solution for injection** should be reconstituted with 1.2 mL sterile water for injections, yielding a deliverable volume of 1 mL. An additional overfill is included in each vial to ensure that 500 mcg of romiplostim can be delivered (see vial content table below).

Vial Content:

Nplate single-use vial	**Total vial content of romiplostim**		**Volume of sterile water for injection**		**Deliverable product and volume**	**Final concentration**
125 mcg	230 mcg	+	0.44 mL	=	125 mcg in 0.25 mL	500 mcg/mL
250 mcg	375 mcg	+	0.72 mL	=	250 mcg in 0.50 mL	500 mcg/mL
500 mcg	625 mcg	+	1.20 mL	=	500 mcg in 1.00 mL	500 mcg/mL

Sterile water for injections only should be used when reconstituting the medicinal product. Sodium chloride solutions or bacteriostatic water should not be used when reconstituting the medicine.

Water for injections should be injected into the vial. The vial contents may be swirled gently and inverted during dissolution. **The vial should not be shaken or vigorously agitated.** Generally, dissolution of Nplate takes less than 2 minutes. Visually inspect the solution for particulate matter and discolouration before administration. The reconstituted solution should be clear and colourless and should not be administered if particulate matter and/or discolouration are observed.

From a microbiological point of view, the medicine should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 25°C or 24 hours in a refrigerator (2°C – 8°C), protected from light.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

Dilution (required when the calculated individual patient dose is less than 23 mcg)

Initial reconstitution of romiplostim with designated volumes of sterile water for injections results in a concentration of 500 mcg/mL in all vial sizes. If the calculated individual patient dose is less than 23 mcg, an additional dilution step to 125 mcg/mL with **preservative-free, sterile, sodium chloride 9 mg/mL (0.9%) solution for injection** is required to ensure accurate volume (see table below).

Dilution Guidelines:

Nplate single-use vial	Add this volume of preservative-free, sterile, sodium chloride 9 mg/mL (0.9%) solution for injection to the **reconstituted vial**	Concentration after dilution
125 mcg	1.38 mL	125 mcg/mL
250 mcg	2.25 mL	125 mcg/mL
500 mcg	3.75 mL	125 mcg/mL

Preservative-free, sterile, sodium chloride 9 mg/mL (0.9%) solution for injection only must be used for dilution. Dextrose (5%) in water or sterile water for injection should not be used for the dilution. No other diluents have been tested.

From a microbiological point of view, the diluted medicinal product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 4 hours at 25°C in disposable syringes, or 4 hours in a refrigerator (2°C – 8°C) in the original vials, protected from light.