Package leaflet: Information for the user

NULOJIX 250 mg powder for concentrate for solution for infusion
belatacept

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 or pharmacist.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What NULOJIX is and what it is used for
2. What you need to know before you use NULOJIX
3. How to use NULOJIX
4. Possible side effects
5. How to store NULOJIX
6. Contents of the pack and other information

1. What NULOJIX is and what it is used for

NULOJIX contains the active substance belatacept which belongs to a group of medicines called immunosuppressants. These are medicines that reduce the activity of the immune system, the body's natural defences.

NULOJIX is used in adults to prevent the immune system from attacking your transplanted kidney and causing transplant rejection. It is used with other immunosuppressive medicines, including mycophenolic acid and corticosteroids.

2. What you need to know before you use NULOJIX

Do not use NULOJIX
- **If you are allergic** to belatacept or any of the other ingredients of the medicine (listed in section 6). Allergic reactions related to belatacept use have been reported in the clinical studies.
- **If you have not been exposed to the Epstein-Barr virus** (EBV) or are uncertain of previous exposure, you must not be treated with NULOJIX. EBV is the virus that causes glandular fever. If you have not been exposed to it, you are at a higher risk of getting a type of cancer called post-transplant lymphoproliferative disorder (PTLD). If you are not sure if you have been infected with the virus before, ask your doctor.

Warnings and precautions
Post-transplant lymphoproliferative disorder
Treatment with NULOJIX increases the risk of getting a type of cancer called post-transplant lymphoproliferative disorder (PTLD). With NULOJIX treatment, this more often develops in the brain and can lead to death. People are at a higher risk of developing PTLD in the following cases:
- If you have not been exposed to EBV prior to your transplant
- If you are infected with a virus called cytomegalovirus (CMV)
- If you have been given a therapy for treatment of acute rejection, such as antithymocyte globulin to reduce T-cells. T-cells are cells responsible for maintaining your body's ability to resist disease and infections. They may cause rejection of your transplanted kidney.
- If you are not sure about any of these conditions, ask you doctor.

Serious infections
Serious infections can happen with NULOJIX treatment and can lead to death.
NULOJIX weakens the body's ability to fight infections. Serious infections can include
- Tuberculosis
- Cytomegalovirus (CMV), a virus that can cause serious tissue and blood infections
- Shingles
- Other herpes virus infections.

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

Tell your family or caregiver about your treatment. You might get symptoms that you might not be aware of yourself. Your doctor may need to investigate your symptoms to rule out PML, PTLD or other infections. For a list of symptoms please see section 4, "Possible side effects".

Skin cancer
Limit your exposure to sunlight and ultraviolet (UV) light whilst using NULOJIX. Wear protective clothing and use a sunscreen with a high protection factor. People who use NULOJIX have a higher risk of getting certain other types of cancer, especially skin cancer.

Blood clotting in your transplanted kidney
Depending on the type of kidney transplant that you received, you may be at higher risk of blood clotting in your transplanted kidney.

Use in conversion from another type of immunosuppressive maintenance treatment
If your healthcare professional changes your maintenance treatment to a NULOJIX based immunosuppressive regimen, he/she may check your kidney function more often for a period of time after the change, to monitor for rejection.

Use in liver transplants
The use of NULOJIX is not recommended if you have had a liver transplant.

Use with other immunosuppressive medicines
Nulojix is normally given with steroids. Too rapid reduction of steroid intake can increase the risk that your body may reject the transplanted kidney. Please take the exact steroid dose as determined by your doctor.

Children and adolescents
NULOJIX has not been studied in children and adolescents under 18 years of age, therefore it is not recommended in this age group.

Other medicines and NULOJIX
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. Ask your doctor or pharmacist for advice before taking any other medicine while using NULOJIX.

The use of live vaccines should be avoided with the use of NULOJIX. Tell your doctor if you need to have vaccinations. Your doctor will advise you what to do.

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.
If you become pregnant while using NULOJIX, tell your doctor.
Do not use NULOJIX if you are pregnant unless your doctor specifically recommends it. The effects of NULOJIX in pregnant women are not known. You must not get pregnant while using NULOJIX. If you are of child bearing potential, you should use effective contraception during treatment with NULOJIX and up to 8 weeks after the last dose of treatment since the potential risk to

embryonic/foetal development is unknown. Your doctor will advise you about using a reliable contraceptive.

You must stop breast-feeding if you are being treated with NULOJIX. It is not known whether belatacept, the active substance, passes into human milk.

Driving and using machines
Belatacept has a minor influence on the ability to drive and use machines. However you should not drive or operate any machines if you are feeling tired or unwell after receiving NULOJIX.

NULOJIX contains sodium
Tell your doctor if you are on a low-sodium (low-salt) diet before you are treated with NULOJIX. This medicine contains 0.55 mmol (or 13 mg) sodium per vial. This is equivalent to 0.64% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use NULOJIX

Treatment with NULOJIX will be prescribed and supervised by a specialist in kidney transplantation. NULOJIX will be given to you by a healthcare professional.

It will be given to you by infusion (as a "drip") into one of your veins over a period of about 30 minutes.

The recommended dose is based on your body weight (in kg) and will be calculated by a healthcare professional. The dose and treatment frequency is given below.

Initial Phase	Dose
Day of transplantation, prior to implantation (Day 1) Day 5, Day 14 and Day 28 End of Week 8 and Week 12 after transplantation	10 mg/kg
Maintenance Phase	**Dose**
Every 4 weeks (± 3 days) starting at end of week 16 after transplantation	6 mg/kg

At the time of your kidney transplant you may be given NULOJIX in combination with other types of immunosuppressant medication to help prevent your body from rejecting your transplanted kidney.

Your doctor may decide to change your immunosuppressive treatment to a treatment with NULOJIX during the maintenance phase after your kidney transplant.

Information for medical and healthcare professionals on dose calculation, preparation and administration of NULOJIX is provided at the end of the leaflet.

If you are given more NULOJIX than you should
If this happens, your doctor will monitor you for any signs or symptoms of side effects, and treat these symptoms if necessary.

If you forget to use NULOJIX
It is very important for you to keep all appointments to receive NULOJIX. If you miss receiving NULOJIX when you are supposed to, ask your doctor when to schedule your next dose.

If you stop using NULOJIX
Your body may reject the transplanted kidney if you stop using NULOJIX. The decision to stop using NULOJIX should be discussed with your doctor and another therapy will generally be started.
If you stop treatment with NULOJIX for a long period of time, without taking any other medicines to prevent rejection, and then restart, it is not known if belatacept will have the same effect as before.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. However, NULOJIX can cause serious side effects that may need treatment.
Tell your family or caregiver about your treatment as you might get symptoms that you might not be aware of yourself.

Tell your doctor immediately if you or your family notice any symptoms listed below:

Nervous system symptoms may include memory lapse; speech and communication difficulties; a change in your mood or behaviour; confusion or inability to control your muscles; weakness on one side of the body; vision changes; or headache.

Infection symptoms may include fever; unexplained weight loss; swollen glands; cold symptoms such as a runny nose or sore throat; cough with sputum; blood in your sputum; earache; cuts or scrapes that are red; warm and oozing pus.

Kidney or bladder symptoms may include tenderness at the site of your transplanted kidney; difficulty passing urine; changes in the amount of urine you produce; blood in the urine; pain or burning on urination.

Gastrointestinal symptoms may include pain on swallowing; painful mouth ulcers; white patches in the mouth or throat; upset stomach; stomach pain; vomiting; or diarrhoea.

Skin changes may include unexpected bruising or bleeding; brown or black skin lesion with uneven borders, or one part of the lesion does not look like the other; a change in the size and colour of a mole; or a new skin lesion or bump.

Allergic reactions may include, but are not limited to, rash; reddened skin; hives; itching; lip swelling; tongue swelling; swelling of the face; swelling over entire body; chest pain; shortness of breath; wheezing; or dizziness..

Very common side effects (may affect more than 1 in 10 people**) are:**
- Bladder or kidney infection, upper respiratory infection, CMV infection (can cause serious blood and tissue infections), fever, cough, bronchitis
- Shortness of breath
- Constipation, diarrhoea, nausea, vomiting, abdominal pain
- High blood pressure, low blood pressure
- Headache, difficulty sleeping, feeling nervous or anxious, swelling of the hands and feet
- Joint pain, back pain, pain in the extremities
- Pain when passing urine, blood in the urine

Tests may show:
- Low blood count or anaemia, low white blood cell count
- Increased amounts of creatinine in your blood (blood test used to measure kidney function), increased amounts of protein in your urine
- Changes in blood levels of different salts or electrolytes
- Increased amounts of cholesterol and triglyceride (blood fats)
- High levels of sugar in your blood

Common side effects (may affect up to 1 in 10 people**) are:**
- Cancer and non-cancerous growths of the skin
- Dangerous decrease of blood pressure which, if untreated, may lead to collapse, coma and death
- Stroke
- Dead tissue because of stopped blood supply

- Liver inflammation (cytolytic hepatitis)
- Damage to the kidney
- Fluid in the lungs, wheezing, chest pain or angina, enlarged heart muscle (bottom of the heart)
- Infection of the blood or tissues, respiratory infections, pneumonia, flu, sinus inflammation, runny nose, sore throat, pain in the mouth/throat region, herpes virus infections, shingles and other viral infections, mouth sores, thrush, kidney infection, fungal skin infections,fungal infections of the nails and other fungal infections, skin infection, infection of soft tissues, wound infection, infection limited to one area, slow healing, bloody bruise, build up of lymph fluid around the transplanted kidney
- Fast heart rate, slow heart rate, abnormal and irregular heart beat, weak heart
- Diabetes
- Dehydration
- Inflammation of the stomach and intestines, usually caused by a virus
- Upset stomach
- Unusual sensation of pins and needles, numbness or weakness of the arms and legs
- Rash, itching
- Muscle pain, muscle weakness, bone pain, joint swelling, abnormal cartilage between bones of the spine, sudden inability to bend joint, muscle spasms, arthritis
- Blockage of kidney blood vessels, enlarged kidney due to blockage of urine flow out of the kidney, backflow of urine from the bladder into the kidney tubes, inability to hold urine, incomplete emptying of the bladder, urinating at night, sugar in the urine
- Increase in body weight, decrease in body weight
- Cataract, increased blood congestion in the eye, blurred vision
- Shaking or tremors, dizziness, fainting or passing out, ear pain, buzzing, ringing or other persistent noise in the ears
- Acne, hair loss, abnormal change to the skin, excessive sweating, night sweats
- Weakness/gap in abdominal muscles and out pouching of skin over healed incision, hernia on the stomach wall
- Depression, fatigue, feeling of tiredness, drowsiness, or lack of energy, general feeling of being unwell, difficulty breathing when laying down, nose bleeding
- Typical appearance of a person with high levels of steroids, such as moon face, hump back, upper body obesity
- Abnormal collection of fluid

Tests may show:

- Low platelet counts in your blood, too many white blood cells, too many red blood cells
- Changes in blood levels of carbon dioxide, fluid retention, low protein in the blood
- Abnormal liver function tests, blood parathyroid hormone increased
- Increased protein (c-reactive protein) in blood indicating inflammation
- A decrease of antibodies (proteins that fight infection) in your blood

Uncommon side effects (may affect up to 1 in 100 people**) are:**

- Lung cancer, rectal cancer, breast cancer, a form of cancer in the bones, musles, or fat tissue, tumor of the skin and intestinal tract caused by a herpes virus and seen in patients with a weakened immune system, prostate cancer, cancer of the cervix, throat cancer, cancer of the lymph nodes, cancer of the bone marrow, cancer of the kidney, kidney tubes, or bladder
- Fungal infection of brain, inflammation of the brain, serious brain infection called PML (progressive multifocal leukoencephalopathy)
- Abnormal swelling of the brain, increased pressure inside the skull and brain, seizure, weakness causing loss of movement on one side of the body, loss of the covering around nerves, inability of muscles to move in the face
- Any disease of the brain causing headache, fever, hallucinations, confusion, abnormal speech and body movement
- Poor blood flow to the heart, blocked heart beats, abnormal aorta heart valve, abnormal rapid heart rate
- Sudden problems with breathing leading to lung damage, increased blood pressure in the lungs, inflammation of the lungs, coughing up blood, abnormality of lungs and air tubes delivering air in

and out of lungs, fluid in the sac around the lungs, breathing that stops temporarily during sleep, abnormal speaking sound
- Genital herpes
- Inflammation of the colon (large bowel) caused by the cytomegalovirus, inflammation of the pancreas, ulcer in the stomach, small intestines, or large intestine, blockage of the small intestine, black, tar-like stools, rectal bleeding, abnormal colour of the stool
- Bacterial infections, inflammation or infection of the inner layer of the heart, tuberculosis, bone infection, inflammation of the lymph nodes, chronic dilation of the airways in the lungs with frequent lung infections
- Infection with the strongyloides worm, diarrheal infection with Giardia parasite
- Kidney disease that is caused by a virus (polyomavirus-associated nephropathy), inflammation of the kidneys, scarring of the kidneys, shrinkage of the small tubes in the kidney, inflammation of the bladder with bleeding
- Blood clotting in kidney artery
- Guillian-Barré syndrome (a condition that causes muscle weakness or paralysis)
- EBV (Epstein-Barr virus) lymphoproliferative disease
- Blood clotting in veins, inflamed veins, periodic leg cramps
- Abnormal arteries, scarring of the arteries, clotting in the arteries, narrowing of the arteries, temporary redness of the face/skin, swelling of the face
- Stones in the gallbladder, fluid filled pocket in the liver, fatty liver
- Skin disease with thickened patches of red skin, often with silvery scales, abnormal hair growth, excessive hair breakage, nails breaking, ulcer on the penis
- Abnormal balance of minerals in the body causing bone problems, bone inflammation, abnormal weakening of the bone leading to bone problems, inflammation of the lining of the joints, rare bone condition
- Inflammation of the testicles, an abnormally prolonged penile erection, abnormal cervical cells, breast mass, pain in the testes, ulcer in the female genital area, thinned vaginal walls, infertility or inability to become pregnant, swelling of the scrotum
- Seasonal allergy
- Poor appetite, loss of taste, decreased hearing
- Abnormal dreams, mood swings, abnormal lack of ability to focus and sit still, difficulty understanding or thinking, poor memory, migraine, irritability
- Numbness or weakness from poorly controlled diabetes, changes in the foot from diabetes, inability to keep legs still
- Swelling of back of the eye causing changes in sight, eye inflamed, uncomfortable/increased sensitivity to light, swelling of the eyelid
- Cracking of the corner of the mouth, swollen gums, salivary gland pain
- Increased sexual desire
- Burning sensation
- Reaction to an infusion, scare tissue, inflammation, return of disease, feeling hot, ulcer
- Not making enough urine
- Failure of transplanted organ to work, problems during or after a transfusion, separation of the wound edges before it heals, broken bone, complete tear or separation of tendon, low blood pressure during or after a procedure, high blood pressure during or after a procedure, bruise/collection of blood within the soft tissues after a procedure, pain related to a procedure, headache related to a procedure, bruise of the soft tissue

Tests may show:
- Dangerously low red blood cells, dangerously lowered white cell counts, destruction of red blood cells, blood clotting problems, acid in the blood from diabetes, lack of acid in the blood
- Improper production of hormones by the adrenal glands
- Low vitamin D levels
- Pancreatic enzymes in the blood increased, troponin levels in the blood increased, prostate-specific antigen (PSA) increased, high uric acid levels in the blood, CD-4 lymphocyte cell counts decreased, low blood sugar

Reporting of side effects
If any of the side effects gets serious, please tell your doctor or pharmacist. 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 NULOJIX

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

This medicine will be stored in the healthcare facility where it is administered.

Store in a refrigerator (2 °C – 8 °C).

Store in the original package in order to protect from light.

After reconstitution, the reconstituted solution should be transferred from the vial to the infusion bag or bottle immediately.

After dilution, and from a microbiological point of view, the product should be used immediately. If not used immediately, the solution for infusion may be stored in a refrigerator (2 °C – 8 °C) for up to 24 hours. The solution for infusion may be stored for a maximum of 4 hours of the total 24 hours below 25 °C. Do not freeze.
The NULOJIX infusion must be completed within 24 hours of reconstitution of the powder.

Do not use NULOJIX if you notice any particles or discolouration in the reconstituted or diluted solution.

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 NULOJIX contains

- The active substance is belatacept. Each vial contains 250 mg of belatacept. After reconstitution, each ml of concentrate contains 25 mg of belatacept.
- The other ingredients are sodium chloride, sodium dihydrogen phosphate monohydrate, sucrose, sodium hydroxide (for pH adjustment) and hydrochloric acid (for pH adjustment). (See section 2)

What NULOJIX looks like and contents of the pack

NULOJIX powder for concentrate for solution for infusion (powder for concentrate) is a white to off-white powder that can appear solid or broken into pieces.
Each vial contains 250 mg belatacept.
Packs of either 1 glass vial and 1 syringe or 2 glass vials and 2 syringes.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

Manufacturer:
Swords Laboratories Unlimited Company T/A Bristol-Myers Squibb Cruiserath Biologics
Cruiserath Road, Mulhuddart
Dublin 15, D15 H6EF
Ireland

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The following information is intended for healthcare professionals only:

- Use aseptic technique to make up the vials and dilute the solution for administration.
- Use the silicone-free disposable syringe provided to make up the vials and to add the solution to the infusion. This will avoid aggregate formation.
- Do not shake the vials. This will avoid foam formation.
- The solution for infusion is to be used in conjunction with a sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 µm to 1.2 µm).

Dose selection and reconstitution of the vials
Calculate the dose and number of NULOJIX vials required. Each NULOJIX vial provides 250 mg of belatacept.

- Total dose of belatacept in mg equals the patient weight in kg times the belatacept dose in mg/kg (6 or 10 mg/kg, see section 3)
- Dose modification of NULOJIX is not recommended for a change in body weight of less than 10%.
- Number of vials required equals the belatacept dose in mg divided by 250 rounded up to the next full number of vials.
- Make up each vial with 10.5 ml reconstitution solution.
- Volume of the reconstituted solution required (ml) equals total belatacept dose in mg divided by 25.

Practical details on the reconstitution of vials
Using aseptic technique, make up each vial with 10.5 ml of one of the following solvents (sterile water for injections, sodium chloride 9 mg/ml (0.9%) solution for injection or 5% glucose solution for injection), using the co-packed disposable syringe (necessary to avoid aggregate formation) and an 18-21 gauge needle. Syringes are marked in units of 0.5 ml; therefore, the calculated dose should be rounded to the nearest 0.5 ml.

Remove the flip off seal from the vial and wipe the top with an alcohol swab. Insert the syringe needle into the vial through the centre of the rubber stopper. Direct the stream of fluid to the glass wall of the vial and not into the powder. Remove the syringe and needle after 10.5 ml of reconstitution fluid has been added to the vial.

To minimise foam formation, gently swirl and invert the vial for at least 30 seconds or until the powder is completely dissolved. Do not shake. Although some foam may remain on the surface of the reconstituted solution, a sufficient excess of belatacept is included in each vial to account for withdrawal losses. Thus, 10 ml of a 25 mg/ml belatacept solution can be withdrawn from each vial.

The reconstituted solution should be clear to slightly opalescent and colourless to pale yellow. Do not use if opaque particles, discolouration or other foreign particles are present. It is recommended to transfer the reconstituted solution from the vial to the infusion bag or bottle immediately.

Practical details on the preparation of the solution for infusion
After reconstitution, dilute the product to 100 ml with sodium chloride 9 mg/ml (0.9%) solution for injection or 5% glucose solution for injection. From a 100 ml infusion bag or bottle (typically, an infusion volume of 100 ml will be appropriate for most patients and doses, but total infusion volume ranging from 50 ml to 250 ml may be used), withdraw a volume of sodium chloride 9 mg/ml (0.9%) solution for injection or 5% glucose solution for injection equal to the volume (ml equals total dose in mg divided by 25) of the reconstituted NULOJIX solution required to provide the dose and discard it. Slowly add the required amount of reconstituted NULOJIX solution from each vial to the infusion bag or bottle using the same disposable syringe used for reconstitution of the powder. Gently mix the infusion container. The concentration of belatacept in the infusion should be between 2 mg and 10 mg belatacept per ml solution.

Any unused portion in the vials must be discarded in accordance with local requirements.

Administration
When reconstitution and dilution are performed under aseptic conditions, the NULOJIX infusion should be started immediately or must be completed within 24 hours of reconstitution of the powder. If not used immediately, the solution for infusion may be stored in the refrigerator (2 °C – 8 °C) for up to 24 hours. Do not freeze. The solution for infusion may be stored for a maximum of 4 hours of the total 24 hours below 25 °C. Infusion must be completed within 24 hours of reconstitution of the powder. Prior to administration, the solution for infusion should be inspected visually for particulate matter or discolouration. Discard the solution if any particulate matter or discolouration is observed. The entire, fully diluted infusion should be administered over a period of 30 minutes and must be administered with an infusion set and a sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 µm to 1.2 µm). Following administration, it is recommended that the intravenous line be flushed with infusion fluid to ensure administration of the complete dose.

NULOJIX should not be infused concomitantly in the same intravenous line with other agents. No physical or biochemical compatibility studies have been conducted to evaluate the coadministration of NULOJIX with other agents.

Do not store any unused portion of the solution for infusion for reuse.

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