

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

NULOJIX 250 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 250 mg of belatacept.

After reconstitution, each ml of concentrate contains 25 mg belatacept.

Belatacept is a fusion protein produced in Chinese hamster ovary cells by recombinant DNA technology.

Excipient with known effect

Each vial contains 0.65 mmol sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate).

The powder is a white to off-white whole or fragmented cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NULOJIX, in combination with corticosteroids and a mycophenolic acid (MPA), is indicated for prophylaxis of graft rejection in adults receiving a renal transplant (see section 5.1 for data on renal function). It is recommended to add an interleukin (IL)-2 receptor antagonist for induction therapy to this belatacept-based regimen.

4.2 Posology and method of administration

Treatment should be prescribed and supervised by specialist physicians experienced in the management of immunosuppressive therapy and of renal transplant patients.

Belatacept has not been studied in patients with Panel Reactive Antibody (PRA) > 30% (who often require increased immunosuppression). Because of the risk of a high total burden of immunosuppression, belatacept should only be used in these patients after consideration of alternative therapy (see section 4.4).

Posology

The recommended dose is based on patient body weight (kg). The dose and treatment frequency is given below.

Table 1: Dose of belatacept for renal transplant recipients

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

For more details on the dose calculation, see section 6.6.

Patients do not require pre-medication prior to administration of belatacept.

NULOJIX should be administered in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids. Corticosteroid tapering in patients taking belatacept should be implemented cautiously, particularly in patients with 4 to 6 human leukocyte antigen (HLA) mismatches (see sections 4.4 and 5.1)

Infusion-related reactions have been reported with belatacept administration in clinical studies. If any serious allergic or anaphylactic reaction occurs, belatacept therapy should be discontinued immediately and appropriate therapy initiated (see section 4.4).

Therapeutic monitoring of belatacept is not required.

During clinical studies, there was no dose modification of belatacept for a change in body weight of less than 10%.

Special populations

Elderly patients

No dose adjustment is required (see sections 5.1 and 5.2).

Renal impairment

No dose adjustment is recommended in patients with renal impairment or undergoing dialysis (see section 5.2).

Hepatic impairment

No patients with hepatic impairment were studied in renal transplant protocols, therefore dose modification of belatacept in hepatic impairment can not be recommended.

Paediatric population

The safety and efficacy of belatacept in children and adolescents 0 to 18 years of age have not yet been established. No data are available.

Method of administration

NULOJIX is for intravenous use only.

The diluted solution must be administered as an intravenous infusion at a relatively constant rate over 30 minutes. Infusion of the first dose should be given in the immediate preoperative period or during surgery, but before completion of the transplant vascular anastomoses.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Transplant recipients who are Epstein-Barr virus (EBV) seronegative or serostatus unknown.

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see section 4.4).

4.4 Special warnings and precautions for use

Post-transplant lymphoproliferative disorder (PTLD)

In the Phase 2 and 3 studies (3 studies), the incidence of PTLD was higher in belatacept-treated patients than in ciclosporin-treated patients (see section 4.8). Belatacept-treated transplant recipients who are EBV seronegative are at an increased risk for PTLD compared with those who are EBV positive (see section 4.8). EBV serology should be ascertained before starting administration of belatacept. Transplant recipients who are EBV seronegative or serostatus unknown should not receive belatacept (see section 4.3).

In addition to EBV seronegative status, other known risk factors for PTLD include cytomegalovirus (CMV) infection and T-cell-depleting therapy, which was more commonly used to treat acute rejection in belatacept-treated patients in Phase 3 clinical studies (see section 5.1).

PTLD in belatacept-treated patients most often presented in the central nervous system (CNS). Physicians should consider PTLD in the differential diagnosis in patients with new or worsening neurologic, cognitive or behavioural signs or symptoms.

Infections

Use of immunosuppressants, including belatacept, can increase susceptibility to infection, including fatal infections, opportunistic infections, tuberculosis, and herpes (see progressive multifocal leukoencephalopathy (PML) warning below and also section 4.8).

CMV prophylaxis is recommended for at least 3 months after transplantation, particularly for patients at increased risk for CMV infection. Pneumocystis pneumonia prophylaxis is recommended for at least 6 months following transplantation.

Tuberculosis was more frequently observed in patients receiving belatacept than ciclosporin in clinical studies (see section 4.8). The majority of cases of tuberculosis occurred in patients who currently live or previously lived in countries with a high prevalence of tuberculosis. Patients should be evaluated for tuberculosis and tested for latent infection prior to initiating belatacept. Adequate treatment of latent tuberculosis infection should be instituted prior to belatacept use.

Progressive multifocal leukoencephalopathy

PML is a rare, often rapidly progressive and fatal, opportunistic infection of the CNS that is caused by the John Cunningham (JC) virus. In clinical studies with belatacept, 2 cases of PML were reported in patients receiving belatacept at doses higher than the recommended regimen. In the renal transplant studies of belatacept, one case of PML was reported in a patient who received an IL-2 receptor antagonist, mycophenolate mofetil (MMF) and corticosteroids as concomitant treatment. In the liver transplant study, the patient received MMF and corticosteroids as concomitant treatment. As an increased risk of PML and of other infections has been associated with high levels of overall immunosuppression, the recommended doses of belatacept and concomitant immunosuppressives, including MMF or MPA, should not be exceeded (see section 4.5).

Early diagnosis and treatment may mitigate the impact of PML. Physicians should consider PML in the differential diagnosis in patients with new or worsening neurologic, cognitive or behavioural signs or symptoms. PML is usually diagnosed by brain imaging, including magnetic resonance imaging (MRI) or computed tomography (CT) scan, and cerebrospinal fluid (CSF) testing for JC viral DNA by polymerase chain reaction (PCR). When the clinical suspicion for PML is high, brain biopsy should be

considered in subjects if the diagnosis of PML cannot be established via CSF PCR and neuroimaging. Consultation with a neurologist is recommended for any suspected or confirmed cases of PML.

If PML is diagnosed, reduction or withdrawal of immunosuppression is recommended taking into account the risk to the graft. Plasmapheresis may accelerate removal of belatacept.

Malignancies

In addition to PTLT, patients receiving immunosuppressive regimens, including belatacept, are at increased risk of malignancies, including skin cancer (see section 4.8). Exposure to sunlight and ultraviolet (UV) light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Graft thrombosis

In clinical trials, an increased incidence of graft thrombosis was observed in the post-transplant period in recipients of extended criteria donor allografts. In postmarketing experience in patients with other predisposing risk factors for thrombosis of the renal allograft, renal allograft thrombosis has occurred when the initial dose of anti-thymocyte globulin, as immunosuppressive induction, was coadministered at the same or nearly the same time with the first dose of belatacept. (see section 4.8).

Liver transplantation

The safety and efficacy of belatacept have not been established in liver transplant patients, and therefore such use is not recommended. In a single Phase 2 clinical study in *de novo* liver transplant patients, an increase in the number of deaths was observed in 2 of 3 belatacept-containing regimens studied. These belatacept dosing regimens differed from those studied in renal transplant recipients (see section 5.1).

Concomitant use with other immunosuppressive agents

Belatacept has been administered with the following immunosuppressive agents in clinical studies: basiliximab, an MPA and corticosteroids.

Lymphocyte Depleting Therapies and MPA: As the total burden of immunosuppression is a risk factor for malignancies and opportunistic infections, higher than the recommended doses of concomitant immunosuppressive agents should be avoided. Lymphocyte depleting therapies to treat acute rejection should be used cautiously.

Patients with high PRA often require increased immunosuppression. Belatacept has not been studied in patients with PRA > 30% (see section 4.2).

Corticosteroid Taper: Corticosteroid tapering in patients taking belatacept should be implemented cautiously, particularly in patients at high immunologic risk, such as those with 4 to 6 human leukocyte antigen (HLA) mismatches. In postmarketing experience, use of belatacept in conjunction with basiliximab induction, mycophenolate mofetil and corticosteroid taper to 5 mg/day by Week 6 post-transplant was associated with an increased rate of acute rejection, particularly Grade III rejection. These Grade III rejections occurred in patients with 4 to 6 HLA mismatches (see sections 4.2 and 5.1).

For patients who may be switched from belatacept to another immunosuppressant, physicians should be aware of the 8-10 day half-life of belatacept to avoid potential under- or over-immunosuppression following discontinuation of belatacept.

Allergic reactions

Infusion-related reactions have been reported with belatacept administration in the clinical studies. Patients are not required to be pre-treated to prevent allergic reactions (see section 4.8). Special caution should be exercised in patients with a history of allergic reactions to belatacept or to any of the excipients. Anaphylaxis has been reported during post marketing surveillance (see section 4.8). If any serious allergic or anaphylactic reaction occurs, NULOJIX therapy should be discontinued immediately and appropriate therapy initiated.

Vaccinations

Immunosuppressant therapy may affect response to vaccination. Therefore, during treatment with belatacept, vaccinations may be less effective although this has not been studied in clinical trials. The use of live vaccines should be avoided (see section 4.5).

Autoimmune process

There is a theoretical concern that treatment with belatacept might increase the risk of autoimmune processes (see section 4.8).

Immunogenicity

Although there were few patients that developed antibodies and there was no apparent correlation of antibody development to clinical response or adverse events, the data are too limited to make a definitive assessment (see section 4.8).

The safety and efficacy of retreatment with belatacept has not been studied. The potential impact of pre-existing antibodies to belatacept should be taken into account when considering retreatment with belatacept following prolonged discontinuation, particularly in patients who have not received continuous immunosuppression.

Patients on controlled sodium diet

This medicinal product contains 0.65 mmol or 15 mg sodium per vial. This corresponds to 1.95 mmol (or 45 mg) sodium per maximum dose of 3 vials. This should be taken into consideration when treating patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Belatacept is a fusion protein that is not expected to be metabolised by the cytochrome P450 enzymes (CYPs) and UDP-glucuronosyltransferases (UGTs). Belatacept appears not to have any relevant direct effects on cytokine levels in liver transplant recipients or in healthy volunteers. Belatacept is therefore not expected to affect cytochrome P450 enzymes via effects on cytokines.

Belatacept is not expected to interrupt the enterohepatic recirculation of MPA. At a given dose of MMF, MPA exposure is approximately 40% higher with belatacept coadministration than with ciclosporin coadministration.

Immunosuppressant therapy may affect response to vaccination. Therefore, during treatment with belatacept, vaccinations may be less effective although this has not been studied in clinical trials. The use of live vaccines should be avoided (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential should use effective contraception during treatment with belatacept and up to 8 weeks after the last dose of treatment since the potential risk to embryonic/foetal development is unknown.

Pregnancy

There are no adequate data from use of belatacept in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to embryonal/foetal development at doses up to 16-fold and 19-fold a human 10 mg/kg dose based on AUC. In a pre- and postnatal development study in rats, limited changes in immune function were observed at 19-fold a human 10 mg/kg dose based on AUC (see section 5.3). Belatacept should not be used in pregnant women unless clearly necessary.

Breast-feeding

Studies in rats have shown excretion of belatacept in milk. It is unknown whether belatacept is excreted in human milk (see section 5.3). Women should not breast-feed while on treatment with a belatacept-based regimen.

Fertility

There are no data on use of belatacept and effect on fertility in humans. In rats, belatacept had no undesirable effects on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Belatacept has a minor influence on the ability to drive and use machines since it may cause fatigue, malaise and/or nausea. Patients should be instructed that if they experience these symptoms they should avoid potentially hazardous tasks such as driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

The adverse reaction profile associated with immunosuppressive agents is often difficult to establish due to the underlying disease and the concurrent use of multiple medicinal products.

The most common serious adverse reactions ($\geq 2\%$) reported with belatacept in both regimens (more intensive [MI] and less intensive [LI]) cumulative up to Year 3 were urinary tract infection, CMV infection, pyrexia, increased blood creatinine, pyelonephritis, diarrhoea, gastroenteritis, graft dysfunction, leukopenia, pneumonia, basal cell carcinoma, anaemia, dehydration.

The most commonly reported adverse reactions ($\geq 20\%$) among patients treated with both belatacept-based regimens (MI and LI) up to Year 3 are diarrhoea, anaemia, urinary tract infection, peripheral oedema, constipation, hypertension, pyrexia, nausea, graft dysfunction, cough, vomiting, leukopenia, hypophosphataemia, and headache.

Adverse reactions resulting in interruption or discontinuation of belatacept in $\geq 1\%$ of patients up to Year 3 were renal vein thrombosis and CMV infection.

Tabulated list of adverse reactions

Presented in Table 2, by system organ classification and frequency categories, is the list of adverse reactions with at least a suspected causal relationship, reported in clinical trials cumulatively up to Year 3 and pooled for both belatacept regimens (MI and LI).

The frequency categories are defined as follows: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$). Within each frequency category adverse reactions are presented in order of decreasing seriousness.

Table 2: Adverse reactions in clinical trials

Infections and infestations	
Very Common	urinary tract infection, upper respiratory infection, cytomegalovirus infection*, bronchitis
Common	sepsis, pneumonia, influenza, gastroenteritis, herpes zoster, sinusitis, herpes simplex, oral candidiasis, pyelonephritis, onychomycosis, BK virus infection, respiratory tract infection, candidiasis, rhinitis, cellulitis, wound infection, localised infection, herpes virus infection, fungal infection, fungal skin infection
Uncommon	progressive multifocal leukoencephalopathy*, cerebral fungal infection, cytomegalovirus (CMV) colitis, polyomavirus-associated nephropathy, genital herpes, staphylococcal infection, endocarditis, tuberculosis*, bronchiectasis, osteomyelitis, strongyloidiasis, blastocystis infection, giardiasis, lymphangitis
Neoplasms, benign, malignant and unspecified (incl cysts and polyps)*	
Common	squamous cell carcinoma of skin, basal cell carcinoma, skin papilloma
Uncommon	EBV associated lymphoproliferative disorder**, lung cancer, rectal cancer, breast cancer, sarcoma, kaposi's sarcoma, prostate cancer, cervix carcinoma, laryngeal cancer, lymphoma, multiple myeloma, transitional cell carcinoma
Blood and lymphatic system disorders	
Very Common	anaemia, leukopenia
Common	thrombocytopenia, neutropenia, leukocytosis, polycythaemia, lymphopenia
Uncommon	monocytopenia, pure red cell aplasia, agranulocytosis, haemolysis, hypercoagulation
Immune system disorders	
Common	blood immunoglobulin G decreased, blood immunoglobulin M decreased,
Uncommon	hypogammaglobulinaemia, seasonal allergy
Endocrine disorders	
Common	cushingoid
Uncommon	adrenal insufficiency
Metabolism and nutrition disorders	
Very Common	hypophosphataemia, hypokalaemia, dyslipidaemia, hyperkalaemia, hyperglycaemia, hypocalcaemia
Common	weight increase, diabetes mellitus, dehydration, weight decrease, acidosis, fluid retention, hypercalcaemia, hypoproteinaemia
Uncommon	diabetic ketoacidosis, diabetic foot, alkalosis, decreased appetite, vitamin D deficiency
Psychiatric disorders	
Very Common	insomnia, anxiety
Common	depression
Uncommon	abnormal dreams, mood swings, attention deficit/hyperactivity disorder, libido increased
Nervous system disorders	
Very Common	headache
Common	tremor, paraesthesia, cerebrovascular accident, dizziness, syncope, lethargy, neuropathy peripheral
Uncommon	encephalitis, Guillain-Barré syndrome*, brain oedema, intracranial pressure increased, encephalopathy, convulsion, hemiparesis, demyelination, facial palsy,

	dysgeusia, cognitive disorder, memory impairment, migraine, burning sensation, diabetic neuropathy, restless leg syndrome
Eye disorders	
Common	cataract, ocular hyperaemia, vision blurred
Uncommon	retinitis, conjunctivitis, eye inflammation, keratitis, photophobia, eyelid oedema
Ear and labyrinth disorders	
Common	vertigo, ear pain, tinnitus
Uncommon	hyposacusis
Cardiac disorders	
Common	tachycardia, bradycardia, atrial fibrillation, cardiac failure, angina pectoris, left ventricular hypertrophy
Uncommon	acute coronary syndrome, atrioventricular block second degree, aortic valve disease, arrhythmia supraventricular
Vascular disorders	
Very Common	hypertension, hypotension
Common	shock, infarction, haematoma, lymphocele, angiopathy, arterial fibrosis
Uncommon	venous thrombosis, arterial thrombosis, thrombophlebitis, arterial stenosis, intermittent claudication, flushing
Respiratory, thoracic and mediastinal disorders	
Very Common	dyspnoea, cough
Common	pulmonary oedema, wheezing, hypocapnea, orthopnoea, epistaxis, oropharyngeal pain
Uncommon	acute respiratory distress syndrome, pulmonary hypertension, pneumonitis, haemoptysis, bronchopneumopathy, painful respiration, pleural effusion, sleep apnoea syndrome, dysphonia, oropharyngeal blistering
Gastrointestinal disorders	
Very Common	diarrhoea, constipation, nausea, vomiting, abdominal pain
Common	dyspepsia, aphthous stomatitis, abdominal hernia
Uncommon	gastrointestinal disorder, pancreatitis, large intestinal ulcer, melaena, gastroduodenal ulcer, rectal haemorrhage, small intestinal obstruction, cheilitis, gingival hyperplasia, salivary gland pain, faeces discoloured
Hepatobiliary disorders	
Common	cytolytic hepatitis, liver function test abnormal
Uncommon	cholelithiasis, hepatic cyst, hepatic steatosis
Skin and subcutaneous tissue disorders	
Common	acne, pruritis, alopecia, skin lesion, rash, night sweats, hyperhidrosis
Uncommon	psoriasis, hair growth abnormal, onychoclasia, penile ulceration, swelling face, trichorrhexis
Musculoskeletal and connective tissue disorders	
Very Common	arthralgia, back pain, pain in extremity
Common	myalgia, muscular weakness, bone pain, joint swelling, intervertebral disc disorder, joint lock, muscle spasms, osteoarthritis
Uncommon	bone metabolism disorder, osteitis, osteolysis, synovitis
Renal and urinary disorders	
Very Common	proteinuria, blood creatinine increased, dysuria, haematuria
Common	renal tubular necrosis, renal vein thrombosis*, renal artery stenosis, glycosuria,

	hydronephrosis, vesicoureteric reflux, urinary incontinence, urinary retention, nocturia
Uncommon	renal artery thrombosis*, nephritis, nephrosclerosis, renal tubular atrophy, cystitis haemorrhagic, kidney fibrosis
Reproductive system and breast disorders	
Uncommon	epididymitis, priapism, cervical dysplasia, breast mass, testicular pain, vulval ulceration, atrophic vulvovaginitis, infertility, scrotal oedema
Congenital, familial and genetic disorders	
Common	hydrocele
Uncommon	hypophosphatasia
General disorders and administration site conditions	
Very Common	oedema peripheral, pyrexia
Common	chest pain, fatigue, malaise, impaired healing
Uncommon	infusion related reaction*, irritability, fibrosis, inflammation, disease recurrence, feeling hot, ulcer
Investigations	
Common	c-reactive protein increased, blood parathyroid hormone increased
Uncommon	pancreatic enzymes increased, troponin increased, electrolyte imbalance, prostate-specific antigen increased, blood uric acid increased, urine output decreased, blood glucose decreased, CD4 lymphocytes decreased
Injury, poisoning and procedural complications	
Very Common	graft dysfunction
Common	chronic allograft nephropathy (CAN), incisional hernia
Uncommon	transplant failure, transfusion reaction, wound dehiscence, fracture, tendon rupture, procedural hypotension, procedural hypertension, post-procedural haematoma, procedural pain, procedural headache, contusion

* See section "Description of selected adverse reactions".

** Includes all events reported over a median of 3.3 years in the Phase 3 studies, and a median of approximately 7 years in the Phase 2 study.

Long-term extension in Study 1 and Study 2

Of the 1209 randomized and transplanted patients in the two Phase 3 studies (see section 5.1), 761 patients continued after Year 3 in a long-term extension period for up to an additional 4 years and continued to receive the study drug according to their original treatment assignment. As compared to the results from the initial 3 years, no new adverse reactions or increasing incidence of adverse reactions (listed above from the initial 3-year period) were detected during the 4-year long-term open label extension.

Description of selected adverse reactions

Malignancies and post-transplant lymphoproliferative disease

Year 1 and 3 frequencies of malignancies are shown in Table 3, except for cases of PTLD which are presented at 1 year and > 3 years (median days of follow-up were 1,199 days for belatacept MI, 1,206 days for belatacept LI, and 1,139 days for ciclosporin). The Year 3 frequency of malignant neoplasms, excluding non-melanoma skin cancers, was similar in the belatacept LI and ciclosporin groups and higher in the belatacept MI group. PTLD occurred at a higher rate in both belatacept treatment groups versus ciclosporin (see section 4.4). Non-melanoma skin cancers occurred less frequently with the belatacept LI regimen than with the ciclosporin or belatacept MI regimens.

Table 3: Malignancies occurring by treatment group (%)

	Up to Year 1			Up to Year 3***		
	Belatacept MI N= 477	Belatacept LI N= 472	Ciclosporin N= 476	Belatacept MI N= 477	Belatacept LI N= 472	Ciclosporin N= 476
Any malignant neoplasm	3.4	1.9	3.4	8.6	5.7	7.1
Non-melanoma skin cancer	1.0	0.2	1.5	4.2	1.5	3.6
Malignant neoplasms excluding non-melanoma skin cancers	2.3	1.7	1.9	4.4	4.2	3.6
PTLD	0.8	0.8	0.2	1.7	1.3	0.6
Malignancies excluding non-melanoma skin cancer and PTLD	1.5	0.8	1.7	2.7	3.2	3.4

*Median follow-up excluding PTLD for pooled studies is 1,092 days for each treatment group.

**Median follow-up for PTLD for pooled studies is 1,199 days for MI, 1,206 days for LI, and 1,139 days for ciclosporin.

In the 3 studies (one Phase 2 and two Phase 3 studies, Study 1 and Study 2), the cumulative frequency of PTLD was higher in belatacept treated patients at the recommended dosing regimen (LI) (1.3%; 6/472) than in the ciclosporin group (0.6%; 3/476), and was highest in the belatacept MI group (1.7%; 8/477). Nine of 14 cases of PTLD in belatacept-treated patients were located in the CNS; within the observation period, 8 of 14 cases were fatal (6 of the fatal cases involved the CNS). Of the 6 PTLD cases in the LI regimen, 3 involved the CNS and were fatal.

EBV seronegative patients receiving immunosuppressants are at a particularly increased risk for PTLD (see sections 4.3 and 4.4). In clinical studies, belatacept-treated transplant recipients with EBV seronegative status were at an increased risk for PTLD compared with those who were EBV positive (7.7%; 7/91 versus 0.7%; 6/810, respectively). At the recommended dosing regimen of belatacept there were 404 EBV positive recipients and 4 cases of PTLD occurred (1.0%); 2 of these presented in the CNS.

During the long-term extension period, malignancies (including PTLD) were reported in 10.3%, 8.4%, and 14.7% of patients in the belatacept MI, belatacept LI, and ciclosporin groups, respectively, in Study 1; and in 19.2%, 13.3% and 16.1% of patients in the belatacept MI, belatacept LI, and ciclosporin groups, respectively, in Study 2. Cases of PTLD varied by serostatus. In Study 1, one additional case of PTLD was reported in the ciclosporin group, in a patient who was EBV seropositive at the time of transplant. In Study 2, among patients who were EBV seropositive at the time of transplant, there was one case of PTLD in each of the three treatment groups. Among Study 2 patients who were EBV seronegative at the time of transplant (for whom use of belatacept is not recommended), there were three cases of PTLD in the belatacept LI group, and none in the belatacept MI and ciclosporin groups.

Infections

Year 1 and Year 3 frequencies of infections occurring by treatment group are shown in Table 4. The overall occurrence of tuberculosis infections and non-serious herpes infections were higher for belatacept regimens than for the ciclosporin regimen. The majority of cases of tuberculosis occurred in patients who currently live or previously lived in countries with a high prevalence of tuberculosis (see section 4.4). Overall occurrences of polyoma virus infections and fungal infections were numerically lower in the belatacept LI group compared with the belatacept MI and ciclosporin groups.

Within the belatacept clinical program, there were 2 patients diagnosed with PML. One fatal case of PML was reported in a renal transplant recipient treated with belatacept MI regimen, an IL-2 receptor antagonist, MMF, and corticosteroids for 2 years in a Phase 3 trial. The other case of PML was reported in a liver transplant recipient in a Phase 2 trial who received 6 months of treatment with an augmented belatacept MI regimen, MMF at doses higher than the recommended dose and corticosteroids (see section 4.4).

Infections involving the CNS were more frequent in the belatacept MI group (8 cases, including the PML case discussed above; 1.7%) than the belatacept LI (2 cases, 0.4%) and ciclosporin (one case; 0.2%) groups. The most common CNS infection was cryptococcal meningitis.

Table 4: Infections occurring by treatment group (%)

	Up to Year 1			Up to Year 3*		
	Belatacept MI N= 477	Belatacept LI N= 472	Ciclosporin N= 476	Belatacept MI N= 477	Belatacept LI N= 472	Ciclosporin N= 476
Infections and infestations	70.7	71.8	73.7	79.2	82.0	80.6
Serious infections	26.8	23.3	27.3	35.8	33.5	37.8
Viral infections	26.4	25.0	27.7	38.8	39.0	36.1
CMV	11.1	11.9	13.7	13.8	13.8	14.7
Polyomavirus	4.8	2.3	4.8	6.3	3.8	5.7
Herpes	8.0	6.6	6.1	15.5	14.2	10.7
Fungal infections	13.8	11.0	15.1	22.9	16.7	20.6
Tuberculosis	0.4	0.4	0.2	1.3	1.3	0.2

*Median exposure for pooled studies is 1,092 days for each treatment group.

During the long-term extension period, serious infections occurred in 30.3% and 23.5% of patients in the belatacept MI and LI groups, respectively, and in 27.2% of patients in the ciclosporin group in Study 1; and in 35.6% and 38.1% of patients in the belatacept MI and LI groups, respectively, and in 37.9% of patients in the ciclosporin group in Study 2. There was one case of PML reported (Study 1) in the ciclosporin group at 82 months post-transplant (more than 56 days after discontinuing therapy).

Graft thrombosis

In a Phase 3 study in recipients of extended criteria donor (ECD) kidneys (Study 2), graft thrombosis occurred more frequently in the belatacept groups (4.3% and 5.1% for the MI and LI regimens respectively), versus 2.2% for ciclosporin. In another Phase 3 study in recipients of living donor and standard criteria deceased donor kidneys (Study 1), the incidence of graft thrombosis was 2.3% and 0.4% for the MI and LI regimens respectively, versus 1.8% for ciclosporin. In a Phase 2 study, there were 2 cases of graft thrombosis, 1 each in MI and LI (incidence of 1.4% for both) versus 0 in the ciclosporin group. In general, these events occurred early and the majority resulted in graft loss. In postmarketing experience in patients with other predisposing risk factors for thrombosis of the renal allograft, renal allograft thrombosis has been reported when the initial dose of anti-thymocyte globulin was coadministered at the same or nearly the same time with the first dose of belatacept. (see section 4.4).

Infusion-related reactions

Anaphylaxis has been reported post marketing(see section 4.4).

Acute infusion-related reactions (reactions occurring within one hour of infusion) occurred in 5.5% of patients in the belatacept MI group and 4.4% of patients in the belatacept LI group up to Year 3. The most frequently reported acute infusion-related reactions in combined belatacept regimens were hypotension, hypertension, flushing and headache. Most events were not serious, were mild to moderate in intensity, and did not recur. When belatacept was compared to placebo infusions, there

were no differences in event rates (placebo infusions were administered at Weeks 6 and 10 of the belatacept LI regimen to blind the MI and LI regimens).

Immunogenicity

Antibodies directed against the belatacept molecule were assessed in 796 kidney transplant recipients (551 of these treated for at least 3 years) in the two Phase 3 studies. An additional 51 patients were treated for an average of 7 years in the long-term extension of a Phase 2 study. Anti-belatacept antibody development was not associated with altered clearance of belatacept.

A total of 45 of 847 patients (5.3%) developed antibodies during treatment with belatacept. In the individual studies, the percentage of patients with antibodies ranged from 4.5% and 5.2% in the Phase 3 studies to 11.8% in the long-term extension of the Phase 2 study. However, immunogenicity rate normalised for duration of exposure was consistent at 2.0 to 2.1 per 100 patient years among the three studies. In 153 patients assessed for antibodies at least 56 days (approximately 7 half-lives) after discontinuation of belatacept, an additional 10 (6.5%) developed antibodies. In general, antibody titers were low, not usually persistent, and often became undetectable with continued treatment.

To assess for the presence of neutralising antibodies, samples from 29 patients with confirmed binding activity to the modified cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) region of the molecule were assessed by an in vitro assay; 8 (27.6%) patients were shown to possess neutralising antibodies. The clinical relevance of such antibodies is unclear.

Autoimmunity

The occurrence of autoimmune events across the core clinical studies was infrequent, occurring at rates of 1.7%, 1.7%, and 1.9% by Year 3 for the MI, LI, and ciclosporin groups respectively. One patient on belatacept MI regimen developed Guillian-Barré syndrome which led to treatment discontinuation and subsequently resolved. Overall, the few reports across clinical studies suggest that prolonged exposure to belatacept does not predispose patients to an increased risk of development of autoimmune events.

During the long-term extension period, autoimmune events occurred in 2.6% and 3.0% of patients in the belatacept MI and LI groups, respectively, and in 3.7% of patients in the ciclosporin group in Study 1; and in 5.8% and 3.5% of patients in the belatacept MI and LI groups, respectively, and in 0% of patients in ciclosporin group in Study 2.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

4.9 Overdose

Single doses up to 20 mg/kg have been administered without apparent toxic effect. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants, ATC code: L04AA28.

Belatacept, a selective costimulation blocker, is a soluble fusion protein consisting of a modified extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) fused to a

portion (hinge-CH2-CH3 domains) of the Fc domain of a human immunoglobulin G1 antibody. Belatacept is produced by recombinant DNA technology in a mammalian cell expression system. Two amino acid substitutions (L104 to E; A29 to Y) were made in the ligand binding region of CTLA-4.

Mechanism of action

Belatacept binds to CD80 and CD86 on antigen presenting cells. As a result, belatacept blocks CD28 mediated co-stimulation of T cells inhibiting their activation. Activated T cells are the predominant mediators of immunologic response to the transplanted kidney. Belatacept, a modified form of CTLA4-Ig, binds CD80 and CD86 more avidly than the parent CTLA4-Ig molecule from which it is derived. This increased avidity provides a level of immunosuppression that is necessary for preventing immune-mediated allograft failure and dysfunction.

Pharmacodynamic effects

In a clinical study, approximately 90% saturation of CD86 receptors on the surface of antigen-presenting cells in the peripheral blood was observed following the initial administration of belatacept. During the first month post-transplantation, 85% saturation of CD86 was maintained. Up to month 3 post-transplantation with the recommended dosing regimen, the level of CD86 saturation was maintained at approximately 70% and at month 12, approximately 65%.

Clinical efficacy and safety

Study 1 and 2: Phase 3 studies in renal transplant recipients

The safety and efficacy of belatacept as part of an immunosuppressive regimen following renal transplantation were assessed in two randomised, partially-blinded, multicenter, 3 year studies with the primary endpoint specified at Year 1. These studies compared two dose regimens of belatacept (MI and LI) with ciclosporin in recipients of standard criteria (Study 1) or extended criteria (Study 2) donor organs. All patients received basiliximab, MMF, and corticosteroids. The more intensive (MI) regimen, which included higher and more frequent dosing during the first 6 months post transplant, resulted in 2-fold higher exposure to belatacept than the less intensive (LI) regimen during Months 2 through 7 post transplant. Efficacy was similar between MI and LI while the overall safety profile was better for the LI. Therefore, the recommended dose of belatacept is the LI dosage regimen.

Study 1: Recipients of Living Donor and Standard Criteria Deceased Donor Kidneys

Standard criteria donor organs were defined as organs from a living donor, or a deceased donor with anticipated cold ischemia time of < 24 hours and not meeting the definition of extended criteria donor organs. Study 1 excluded (1) recipients undergoing a first transplant whose current PRA were $\geq 50\%$; (2) recipients undergoing a retransplantation whose current PRA were $\geq 30\%$; (3) recipients when previous graft loss was due to acute rejection and in case of a positive T-cell lymphocytotoxic cross match.

In this study, 666 patients were enrolled, randomised, and transplanted; 219 to belatacept MI, 226 to belatacept LI, and 221 to ciclosporin. The median age was 45 years; 58% of donor organs were from living patients; 3% were re-transplanted; 69% of the study population was male; 61% of patients were white, 8% were black/African-American, 31% were categorised as of other races; 16% had PRA $\geq 10\%$; and 41% had 4 to 6 HLA mismatches.

The dose of corticosteroids used in all treatment groups was tapered during the first 6 months following transplantation. The median corticosteroid doses administered with the belatacept recommended regimen up to months 1, 3, and 6 were 20 mg, 12 mg and 10 mg, respectively.

Study 2: Recipients of Extended Criteria Donor Kidneys

Extended criteria donors were defined as deceased donors with at least one of the following: (1) donor age ≥ 60 years; (2) donor age ≥ 50 years and other donor comorbidities (≥ 2 of the following: stroke, hypertension, serum creatinine > 1.5 mg/dl); (3) donation after cardiac death or (4) anticipated cold ischemia time of ≥ 24 hours. Study 2 excluded recipients with a current PRA $\geq 30\%$, re-transplanted patients, and in case of a positive T-cell lymphocytotoxic cross match.

In this study, 543 patients were enrolled, randomised, and transplanted; 184 to belatacept MI, 175 to belatacept LI, and 184 to ciclosporin. The median age was 58 years; 67% of the study population was male; 75% of patients were white, 13% were black/African-American, 12% were categorised as of other races; 3% had PRA \geq 10%; and 53% had 4 to 6 HLA mismatches.

The dose of corticosteroids used in all treatment groups was tapered during the first 6 months following transplantation. The median corticosteroid doses administered with the belatacept recommended regimen up to months 1, 3, and 6 were 21 mg, 13 mg and 10 mg, respectively.

Table 5 summarises results for belatacept LI compared with ciclosporin for the co-primary efficacy endpoints of death and graft loss, composite renal impairment, and acute rejection (defined as clinically suspected biopsy proven acute rejection). Patient and graft survival were similar between belatacept and ciclosporin. Fewer patients met the composite renal impairment endpoint and mean GFR was higher with belatacept compared to ciclosporin.

Acute rejection (AR) occurred more frequently with belatacept versus ciclosporin in Study 1 and with similar frequency with belatacept versus ciclosporin in Study 2. Approximately 80% of AR episodes occurred by Month 3 and were infrequent after Month 6. In Study 1, 11/39 belatacept and 3/21 ciclosporin acute rejections were Banff 97 grade \geq IIb by Year 3. In Study 2, 9/33 belatacept and 5/29 ciclosporin acute rejections were Banff 97 grade \geq IIb by Year 3. AR was treated more often with lymphocyte depleting therapy (a risk factor for PTLD; see section 4.4) in the belatacept group than the ciclosporin group. In both studies, in patients with AR by Year 2, donor-specific antibodies, one of the criteria for diagnosis of antibody-mediated rejection, were present in 6% (2/32, Study 2)-8% (3/39, Study 1) and 20% (4/20, Study 1)-26% (7/27, Study 2) in the belatacept and ciclosporin groups by year 3, respectively. By Year 3 recurrent AR was similar across groups ($<$ 3%) and subclinical AR identified on the 1 year protocol biopsy was 5% in both groups. In Study 1, 5/39 belatacept patients versus 1/21 ciclosporin patients with AR had experienced graft loss, and 5/39 belatacept patients and no ciclosporin patients with AR had died by Year 3. In Study 2, 5/33 belatacept patients versus 6/29 ciclosporin patients with AR had experienced graft loss, and 5/33 belatacept patients versus 5/29 ciclosporin patients with AR had died by Year 3. In both studies, mean GFR following AR was similar in belatacept and ciclosporin treated patients.

Table 5: Key efficacy outcomes at years 1 and 3

Parameter	Study 1: living and standard criteria deceased donors		Study 2: extended criteria donors	
	Belatacept LI	Ciclosporin	Belatacept LI	Ciclosporin
	N = 226	N = 221	N = 175	N = 184
Patient and Graft Survival (%)				
Year 1 [95% CI]	96.5 [94.1-98.9]	93.2 [89.9-96.5]	88.6 [83.9-93.3]	85.3 [80.2-90.4]
Year 3 [95% CI]	92.0 [88.5-95.6]	88.7 [84.5-92.9]	82.3 [76.6-87.9]	79.9 [74.1-85.7]
Death (%)				
Year 1	1.8	3.2	2.9	4.3
Year 3	4.4	6.8	8.6	9.2
Graft Loss (%)				
Year 1	2.2	3.6	9.1	10.9
Year 3	4.0	4.5	12.0	12.5
% of Patients meeting Composite renal impairment endpoint at Year 1^a	54.2	77.9	76.6	84.8
P-value	<0.0001	-	<0.07	-
AR (%)				
Year 1 (%) [95% CI]	17.3 [12.3-22.2]	7.2 [3.8-10.7]	17.7 [12.1-23.4]	14.1 [9.1-19.2]
Year 3 (%) [95% CI]	17.3 [12.3-22.2]	9.5 [5.6-13.4]	18.9 [13.1-24.7]	15.8 [10.5-21.0]
Mean Measured GFR^b <i>ml/min/1.73 m²</i>				
Year 1	63.4	50.4	49.6	45.2
Year 2	67.9	50.5	49.7	45.0
Mean Calculated GFR^c <i>ml/min/1.73 m²</i>				
Month 1	61.5	48.1	39.6	31.8
Year 1	65.4	50.1	44.5	36.5
Year 2	65.4	47.9	42.8	34.9
Year 3	65.8	44.4	42.2	31.5

^aProportion of Patients with Measured GFR < 60 ml/min/1.73 m² or with a Decrease in Measured GFR ≥ 10 ml/min/1.73 m² from Month 3 to Month 12.

^bMeasured GFR was assessed by iothalamate at Year 1 and 2 only

^cCalculated GFR was assessed by MDRD formula at Month 1, Years 1, 2, and 3

Progression of Chronic Kidney Disease (CKD) Staging

In Study 1 by Year 3, mean calculated GFR was 21 ml/min/1.73 m² higher with belatacept, and 10% and 20% of patients reached CKD stage 4/5 (GFR < 30 ml/min/1.73 m²) with belatacept versus ciclosporin, respectively. In Study 2 by Year 3, mean calculated GFR was 11 ml/min/1.73 m² higher with belatacept, and 27% and 44% of patients reached CKD stage 4/5 (GFR < 30 ml/min/1.73 m²) with belatacept versus ciclosporin, respectively.

Chronic Allograft Nephropathy/Interstitial Fibrosis and Tubular Atrophy (IFTA)

The prevalence of CAN/IFTA at Year 1 in Studies 1 and 2, was numerically lower with belatacept than ciclosporin (~ 9.4% and 5%, respectively).

New Onset Diabetes Mellitus and Blood Pressure

In a prespecified pooled analysis of Studies 1 and 2 at Year 1, the incidence of new onset diabetes mellitus (NODM), defined as use of an antidiabetic agent for ≥ 30 days or ≥ 2 fasting plasma glucose values > 126 mg/dl (7.0 mmol/l) post-transplantation, was 5% with belatacept and 10% with ciclosporin. At Year 3, the incidence of NODM was 8% with belatacept and 10% with ciclosporin.

For Studies 1 and 2 at Years 1 and 3, belatacept was associated with 6 to 9 mmHg lower mean systolic blood pressure, approximately 2 to 4 mmHg lower mean diastolic blood pressure, and less use of antihypertensive medicinal products than ciclosporin.

Long-term extension in Study 1 and Study 2

A total of 321 belatacept (MI: 155 and LI: 166) and 136 ciclosporin patients completed 3 years of treatment in Study 1 and entered the 4-year long-term open label extension period (up to 7 years in total). More patients discontinued in the ciclosporin group (32.4%) versus each belatacept group (17.4% and 18.1% in MI and LI groups, respectively) during the long-term extension period. A total of 217 belatacept (MI: 104 and LI: 113) and 87 ciclosporin patients completed 3 years of treatment in Study 2 and entered the 4-year long-term open label extension period (up to 7 years in total). More patients discontinued in the ciclosporin group (34.5%) versus each belatacept group (28.8% and 25.7% for MI and LI groups, respectively) during the long-term extension period.

As compared to ciclosporin and assessed by the hazard ratio (HR) estimates (for death or graft loss) from an ad hoc Cox regression analysis, overall patient and graft survival was higher for belatacept-treated patients in Study 1, HR 0.588 (95% CI: 0.356-0.972) for the MI group and HR 0.585 (95% CI: 0.356-0.961) for the LI group, and comparable across treatment groups in Study 2, HR 0.932 (95% CI: 0.635-1.367) for the MI group and HR 0.944 (95% CI: 0.644-1.383) for the LI group. The overall proportion of patients with death or graft loss was lower in belatacept-treated patients (MI: 11.4%, LI: 11.9%) as compared to ciclosporin-treated patients (17.6%) in Study 1. The overall proportion of patients with death or graft loss was comparable across treatment groups (29.3%, 30.9%, and 28.3% for MI, LI and ciclosporin, respectively) in Study 2. In Study 1, in the MI, LI, and ciclosporin groups, respectively, death occurred in 7.8%, 7.5%, and 11.3% of patients, and graft loss occurred in 4.6%, 4.9%, and 7.7% of patients. In Study 2, in the MI, LI, and ciclosporin groups, respectively, death occurred in 20.1%, 21.1%, and 15.8% of patients, and graft loss occurred in 11.4%, 13.1%, and 15.8% of patients. The higher proportion of deaths in the LI group in Study 2 was mainly due to neoplasms (MI: 3.8%, LI: 7.1%, ciclosporin: 2.3%).

The higher calculated GFR observed in belatacept-treated patients relative to ciclosporin-treated patients during the first 3 years was maintained over the long-term extension period. In Study 1, mean calculated GFR at 7 years was 74.0, 77.9 and 50.7 mL/min/1.73 m² in the belatacept MI, belatacept LI and ciclosporin groups, respectively. In Study 2, mean calculated GFR at 7 years was 57.6, 59.1 and 44.6 mL/min/1.73 m², in the same groups, respectively. The time to death, graft loss, or GFR < 30 mL/min/1.73 m² was analyzed over the 7-year period: in Study 1, approximately 60% reduction in the risk of death, graft loss, or GFR < 30 mL/min/1.73 m² was observed among patients in the belatacept groups as compared with those assigned to ciclosporin. In Study 2, approximately 40% reduction in this risk was observed among patients in the belatacept groups as compared with those assigned to ciclosporin.

Phase 2 liver transplant study

A single, randomised, multi-center, controlled Phase 2 trial of belatacept in *de novo* orthotopic liver transplant recipients was conducted. A total of 250 subjects were randomised to 1 of 5 treatment groups (3 belatacept and 2 tacrolimus groups). The belatacept dosing used in this liver study was higher in all 3 belatacept arms than the belatacept dosing used in the Phase 2 and 3 renal transplant studies.

An excess in mortality and graft loss was observed in the belatacept LI + MMF group and an excess in mortality was observed in the belatacept MI + MMF group. No pattern was identified in the causes of death. There was an increase in viral and fungal infections in the belatacept groups versus the

tacrolimus groups, however overall frequency of serious infections was not different among all treatment groups (see section 4.4).

Elderly

Two hundred seventeen (217) patients 65 years and older received belatacept across one Phase 2 and two Phase 3 renal studies.

Elderly patients demonstrated consistency with the overall study population for safety and efficacy as assessed by patient and graft survival, renal function, and acute rejection.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with belatacept in one or more subsets of the paediatric population in renal transplantation (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetics of belatacept in renal transplant patients and healthy subjects appeared to be comparable. The pharmacokinetics of belatacept was linear and the exposure to belatacept increased proportionally in healthy subjects after a single intravenous infusion dose of 1 to 20 mg/kg. The mean (range) pharmacokinetic parameters of belatacept after multiple intravenous infusions at doses of 5 and 10 mg/kg in renal transplant subjects were: terminal half-life, 8.2 (3.1-11.9) and 9.8 (6.1-15.1) days, respectively; systemic clearance 0.51 (0.33-0.75) and 0.49 (0.23-0.70) ml/h/kg, respectively; and distribution volume at steady state, 0.12 (0.09-0.17) and 0.11 (0.067-0.17) l/kg, respectively. At the recommended dosing regimen, serum concentration generally reached steady-state by Week 8 in the initial phase following transplantation and by Month 6 during the maintenance phase. At Month 1, 4, and 6 post-transplant, the mean (range) trough concentrations of belatacept were 22.7 (11.1-45.2), 7.6 (2.1-18.0), and 4.0 (1.5-6.6) µg/ml, respectively.

Distribution

Based on population pharmacokinetic analysis of 944 renal transplant patients up to 1 year post-transplant, the pharmacokinetics of belatacept were similar at different time periods post-transplant. The trough concentration of belatacept was consistently maintained up to 5 years post-transplant. Minimal systemic accumulation of belatacept occurred upon multiple infusions of 5 or 10 mg/kg doses in renal transplant patients every 4 weeks. The accumulation index for belatacept at steady state is 1.1.

Elimination

Population pharmacokinetic analyses in renal transplant patients revealed that there was a trend toward higher clearance of belatacept with increasing body weight. No clinically relevant effects of age, gender, race, renal function (calculated GFR), diabetes, or concomitant dialysis on clearance of belatacept was identified.

There is no data available in patients with hepatic impairment.

5.3 Preclinical safety data

Belatacept has less activity in rodents than abatacept, a fusion protein that differs from belatacept by two amino acids in the CD80/86 binding domains. Because of abatacept's similarity to belatacept in structure and mechanism of action and its higher activity in rodents, abatacept was used as a more active homolog for belatacept in rodents. Therefore, preclinical studies conducted with abatacept have been used to support the safety of belatacept in addition to the studies conducted with belatacept.

No mutagenicity or clastogenicity was observed with abatacept in a battery of *in vitro* studies. In a mouse carcinogenicity study, increases in the incidence of malignant lymphomas and mammary tumours (in females) occurred. The increased incidence of lymphomas and mammary tumours observed in mice treated with abatacept may have been associated with decreased control of murine leukaemia virus and mouse mammary tumour virus, respectively, in the presence of long-term

immunomodulation. In a six-month and one-year toxicity study in cynomolgus monkeys with belatacept and abatacept, respectively, no significant toxicity was observed. Reversible pharmacological effects consisted of minimal decreases in serum IgG and minimal to severe lymphoid depletion of germinal centers in the spleen and/or lymph nodes. No evidence of lymphomas or preneoplastic morphologic changes was observed in either study. This was despite the presence in the abatacept study of a virus, lymphocryptovirus, known to cause these lesions in immunosuppressed monkeys within the time frame of these studies. The viral status was not determined in the belatacept study but, as this virus is prevalent in monkeys, it was likely present in these monkeys as well. In rats, belatacept had no undesirable effects on male or female fertility. Belatacept was not teratogenic when administered to pregnant rats and rabbits at doses up to 200 mg/kg and 100 mg/kg daily, respectively, representing approximately 16 and 19 times the exposure associated with the maximum recommended human dose (MRHD) of 10 mg/kg based on AUC. Belatacept administered to female rats daily during gestation and throughout the lactation period was associated with infections in a small percentage of dams at all doses (≥ 20 mg/kg, ≥ 3 times the MRHD exposure based on AUC), and produced no adverse effects in offspring at doses up to 200 mg/kg representing 19 times the MRHD exposure based on AUC. Belatacept was shown to cross the placenta in rats and rabbits. Abatacept administered to female rats every three days during gestation and throughout the lactation period, produced no adverse effects in offspring at doses up to 45 mg/kg, representing 3 times the exposure associated with the MRHD of 10 mg/kg based on AUC. However, at 200 mg/kg, 11 times the MRHD exposure, alterations in immune function were observed consisting of a 9-fold increase in T-cell dependent antibody response in female pups and thyroid inflammation in one female pup. It is not known whether these findings indicate a risk for development of autoimmune diseases in humans exposed *in utero* to abatacept or belatacept.

Studies in rats exposed to abatacept have shown immune system abnormalities including a low incidence of infections leading to death (juvenile rats) as well as inflammation of the thyroid and pancreas (both juvenile and adult rats). Studies in adult mice and monkeys have not demonstrated similar findings. It is likely that the increased susceptibility to opportunistic infections observed in juvenile rats is associated with the exposure to abatacept before development of memory responses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Sodium dihydrogen phosphate monohydrate
Sodium chloride
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

NULOJIX should not be used with siliconised syringes in order to avoid aggregate formation (see section 6.6).

6.3 Shelf life

Unopened vials
3 years

After reconstitution

The reconstituted solution should be transferred from the vial to the infusion bag or bottle immediately.

After dilution

Chemical and physical in-use stability of the solution for infusion has been demonstrated for 24 hours when stored in a refrigerator (2°C - 8°C). 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. Out of these 24 hours, the solution for infusion may be stored below 25°C for a maximum of 4 hours. Do not freeze.

The NULOJIX infusion must be completed within 24 hours of reconstitution of the powder.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

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

For storage conditions after reconstitution or dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

NULOJIX is supplied in a 20 ml vial (Type I flint glass) with a stopper (20 mm grey butyl rubber) and flip off seal (aluminum). Each vial is co-packaged with a disposable polypropylene syringe.

Pack sizes: 1 vial and 1 syringe or 2 vials and 2 syringes.

Not all pack-sizes may be marketed.

6.6 Special precautions for disposal and other handling

- Use aseptic technique to reconstitute 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 (see section 6.2).
- 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 (5 or 10 mg/kg, see section 4.2).
- 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 minimize 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 belatacept solution required to provide the dose and discard it. Slowly add the required amount of reconstituted belatacept 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. Do not store any unused portion of the solution for infusion for reuse.

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.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Uxbridge Business Park
Sanderson Road
Uxbridge UB8 1DH
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/694/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 June 2011

Date of latest renewal: 18 February 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency
<http://www.ema.europa.eu>.

ANNEX II

**A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND
MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING
AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND
EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Bristol-Myers Squibb Company
6000 Thompson Road, East Syracuse
New York 13057 – U.S.A.

Name and address of the manufacturer responsible for batch release

Bristol-Myers Squibb S.R.L.
Contrada Fontana del Ceraso
03012 Anagni (FR) - Italy

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- Additional risk minimisation measures

A dedicated Alert Card has been developed to prompt the patient to reference the package leaflet and HCPs to reference the SmPC for more details on the benefits and risks associated with NULOJIX. The distribution of the card will also prompt dialogue on any new or changes in symptoms since the prior visit. This card should be provided in each pack, the text of which is included in Annex III.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

NULOJIX 250 mg powder for concentrate for solution for infusion
belatacept

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 250 mg belatacept.
After reconstitution, each ml of concentrate contains 25 mg belatacept.

3. LIST OF EXCIPIENTS

Excipients: sucrose, sodium dihydrogen phosphate monohydrate, sodium chloride, and for pH adjustment sodium hydroxide and hydrochloric acid. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion

1 vial
1 syringe

2 vials
2 syringes

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Read the package leaflet before use.
Intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Only use co-packed syringe for reconstitution and dilution.

8. EXPIRY DATE

EXP

See leaflet for shelf-life after reconstitution and dilution.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard any unused solution.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Uxbridge Business Park - Sanderson Road
Uxbridge UB8 1DH - United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/694/001
EU/1/11/694/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:

SN:
<NN:>

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING
VIAL LABEL**

1. NAME OF THE MEDICINAL PRODUCT

NULOJIX 250 mg powder for concentrate
belatacept

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 250 mg belatacept.
After reconstitution, each ml of concentrate contains 25 mg belatacept.

3. LIST OF EXCIPIENTS

Excipients: sucrose, sodium dihydrogen phosphate monohydrate, sodium chloride, and for pH adjustment sodium hydroxide and hydrochloric acid. Read the package leaflet before use.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate
250 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Read the package leaflet before use.
Intravenous use.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT
OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Only use co-packed syringe for reconstitution and dilution.

8. EXPIRY DATE

EXP
Read the package leaflet before use.

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Discard any unused solution.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Uxbridge Business Park - Sanderson Road
Uxbridge UB8 1DH - United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/11/694/001
EU/1/11/694/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

NULOJIX Patient Alert Card

You are being treated with a potent medicine that suppresses the immune system. From week 4 after transplant, you will receive treatment with NULOJIX every 4 weeks. Regular administration of NULOJIX is essential for your transplanted kidney to function.

More detailed information on the benefits, risks, and precautions for usage of NULOJIX are described in the Summary of Product Characteristics (SmPC) for health care professionals and a package leaflet (PL) for patients. It is important that you read the entire PL for more information.

Take all medicines as instructed by your doctor.

Please make sure you **have this card with you at all times** and a list of all your other medicines with you at any visit to a healthcare professional.

It is very important to keep all appointments for NULOJIX treatment.

Dates of NULOJIX Treatment:

Start (Day of Transplant): _____

Most recent: _____

Next treatment date: _____

Patient's Name: _____

Doctor's Name: _____

Doctor's Phone: _____

If NULOJIX is stopped, keep this card with you for an additional 3 months.

B. PACKAGE LEAFLET

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.
- Each pack of the medicine contains an alert card that should be given to the patient. This Patient Alert Card includes information that will be helpful to you and alert other doctors that you have a transplanted kidney and are on a potent medicine to keep your kidney working. The card will have your doctor's name and phone number and the date when you started treatment, your last treatment visit, and your next visit for treatment. Keep this Alert Card with you at all times.

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. It is also recommended to administer an interleukin(IL)-2 receptor antagonist during the first week after transplantation.

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 your 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, PTLTD 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 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.

Important information about some of the ingredients of NULOJIX

Tell your doctor if you are on a low-sodium (low-salt) diet before you are treated with NULOJIX. This medicine contains 0.65 mmol (or 15 mg) sodium per vial which corresponds to 1.95 mmol (or 45 mg) sodium per maximum dose of three vials.

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	10 mg/kg
End of Week 8 and Week 12 after transplantation	
Maintenance Phase	Dose
Every 4 weeks (\pm 3 days) starting at end of week 16 after transplantation	5 mg/kg

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, muscles, 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 via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

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

Uxbridge Business Park

Sanderson Road

Uxbridge UB8 1DH

United Kingdom

Manufacturer:

Bristol-Myers Squibb S.R.L.
Contrada Fontana del Ceraso
I-03012 Anagni-Frosinone
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

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 (5 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.