SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Methylprednisolon Eurogenerics 4 mg tabletten
Methylprednisolon Eurogenerics 16 mg tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Methylprednisolon Eurogenerics 4 mg tablets: Each tablet contains 4 mg methylprednisolone
Methylprednisolon Eurogenerics 16 mg tablets: Each tablet contains 16 mg methylprednisolone

Excipients with known effect:
Methylprednisolon Eurogenerics 4 mg tablets: Each tablet contains 36.625 mg of lactose monohydrate and 5.625 mg of sucrose.
Methylprednisolon Eurogenerics 16 mg tablets: Each tablet contains 146.5 mg of lactose monohydrate and 22.5 mg of sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Methylprednisolon Eurogenerics 4 mg tablets:
White to off white, round, 4 mm in diameter, biconvex tablets, plain on both sides.
Methylprednisolon Eurogenerics 16 mg tablets:
White to off white, oval, with a length of 10,10 mm and a height of 7,30 mm, biconvex tablets, breakline on one side and embossed '16' on the other side.

The tablet can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Glucocorticoids should be considered as a purely symptomatic treatment, unless in case of certain endocrine disorders, where they are applied as substitution treatment.

Methylprednisolon Eurogenerics is indicated in the following cases:

NONENDOCRINE DISORDERS

1. Rheumatic disorders
As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:
- Psoriatic arthritis
- Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)
- Ankylosing spondylitis
- Abarticular inflammations (such as acute and subacute bursitis, acute nonspecific tenosynovitis and epicondylitis)
- Acute arthritis (gouty, post-traumatic)

- Synovitis of osteoarthritis

2. Collagen diseases
During an exacerbation or as maintenance therapy in selected cases of:
- Systemic lupus erythematosus
- Systemic dermatomyositis (polymyositis)
- Polymyalgia rheumatica
- Giant cell arteritis

3. Dermatologic disorders
- Pemphigus
- Bullous dermatitis herpetiformis
- Severe erythema multiforme (Stevens-Johnson Syndrome)
- Exfoliative dermatitis
- Mycosis fungoides
- Severe psoriasis
- Severe seborrhoeic dermatitis

4. Allergic disorders
Control of severe or incapacitating allergic conditions intractable to adequate conventional therapies:
- Seasonal or chronic allergic rhinitis
- Serum sickness
- Bronchial asthma
- Drug allergy
- Contact dermatitis
- Atopic dermatitis

5. Ophthalmic disorders
Severe acute and chronic allergic and inflammatory processes involving the eye, such as:
- Allergic corneal marginal ulcers
- Herpes zoster ophthalmicus
- Inflammation of the anterior segment of the eye
- Diffuse posterior uveitis and choroiditis
- Sympathetic ophthalmia
- Allergic conjunctivitis
- Keratitis
- Chorioretinitis
- Optic neuritis
- Iritis and iridocyclitis

6. Respiratory diseases
- Symptomatic pulmonary sarcoidosis
- Loeffler's Syndrome not manageable by other means
- Berylliosis
- Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy
- Pulmonary disorders caused by aspiration

7. Haematologic disorders
- Idiopathic thrombocytopenic purpura in adults
- Secondary thrombocytopenia in adults
- Acquired (autoimmune) haemolytic anaemia
- Erythroblastopenia (aplastic anaemia)
- Congenital hypoplastic anaemia

8. Oncological disorders
- For palliative management of:
  - Leukaemias and lymphomas in adults
  - Acute leukaemia in children

9. Oedematous states
- To induce diuresis or remission of proteinuria in nephrotic syndrome, without uraemia, of the idiopathic type or that due to lupus erythematosus

10. Gastrointestinal disorders
To tide the patient over a critical period of the disease in:
- Ulcerative colitis
- Crohn's disease

11. Neurological disorders
- Acute exacerbations of multiple sclerosis
- Oedema in brain tumours

12. Miscellaneous
- Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy
- Trichinosis with neurologic or myocardial involvement
- Acute rheumatic carditis

13. Organ transplantation

ENDOCRINE DISORDERS
- Primary or secondary adrenocortical insufficiency
  (Hydrocortisone or cortisone is the drug of choice for these indications. Synthetic analogues may be used in conjunction with mineralocorticoids in certain cases; in children, mineralocorticoid supplementation is of particular importance.)
- Congenital adrenal hyperplasia
- Nonsuppurative thyroiditis (De Quervain's thyroiditis)
- Hypercalcaemia as a result of cancer

4.2 Posology and method of administration

Posology
The initial daily dose of Methylprednisolon Eurogenerics tablets ranges between 4 mg and 48 mg of methylprednisolone, depending on the condition being treated.
In situations of less severity lower doses will generally suffice while in selected patients higher initial doses may be required.
Clinical situations in which high dose therapy may be indicated include cerebral oedema (200 - 1,000 mg/day), organ transplantation (up to 7 mg/kg/day) and multiple sclerosis. In the treatment of acute exacerbations of multiple sclerosis, oral methylprednisolone doses of 500 mg/day for 5 days or 1,000 mg/day for 3 days have been shown to be effective.

If, after a reasonable period of time, there is a lack of satisfactory clinical response, Methylprednisolon Eurogenerics should be discontinued and the patient transferred to other appropriate therapy. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

After a favourable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage gradually at appropriate time intervals until the lowest effective maintenance dosage is reached.

Constant monitoring is needed in regard to drug dosage. The situations in which the dosage may need to be adjusted are:
- changes in clinical status secondary to remissions or exacerbations in the disease process
- the patient's individual response to the drug
- the effect of patient exposure to stressful situations not directly related to the disease entity under treatment.

In this latter situation it may be necessary to increase the dosage of methylprednisolone for a period of time consistent with the patient's condition. It should be emphasised that dosage requirements are variable and must be individualised on the basis of the disease under treatment and the response of the patient.

Alternate Day Therapy (ADT)
Alternate day therapy is a corticosteroid dosing regimen in which twice the usual daily dose of corticosteroid is administered every other morning.

The purpose of this mode of therapy is to provide a patient requiring long-term pharmacologic dose treatment with the beneficial effects of corticoids while minimising certain undesirable effects, including pituitary-adrenal suppression, the Cushingoid state, corticoid withdrawal symptoms and growth suppression in children.

Elderly patients
When treatment is envisaged in the elderly, the risk that side effects of corticosteroids may be more serious in the elderly, especially osteoporosis, diabetes mellitus, hypertension, susceptibility to infections and atrophy of the skin, should be taken into account, especially in cases of long-term therapy (see section 4.4).

Paediatric population
The posology in children should be based on the dosage principles in adults (see above) and should be tailored to the severity of the disease and the clinical response. Treatment should be limited to the lowest dose necessary to achieve a positive response in the shortest possible time. If administration of the medicinal product is to be stopped after long-term treatment, it is advisable to reduce the doses gradually rather than to stop treatment abruptly.
If possible, treatment should be administered as a single dose every other day (see above and section 4.4).

Method of administration
Oral administration.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- Acute infections: viral infections and systemic fungal infections (bacterial infections: see section 4.4)
- Gastric and duodenal ulcer
- Tropical worm infections
- Administration of live or live-attenuated vaccines is contraindicated in patients receiving an immunosuppressive dose of corticosteroids or who have received one in the previous 3 months.

4.4 Special warnings and precautions for use

Special risk groups
Patients belonging to the following risk groups should be treated under strict medical supervision and for the shortest possible period: children, diabetics, hypertensive patients, patients with a psychiatric history, patients with ocular herpes simplex or zona with ocular symptoms.
Treatment should generally be limited to the shortest possible time. Medical monitoring is recommended for chronic treatments (see Posology and method of administration).
Long-term treatments should also be reduced under medical supervision (progressive reduction, evaluation of adrenal function). The most important symptoms of adrenal insufficiency are asthenia, orthostatic hypotension and depression.

Thrombosis including venous thromboembolism has been reported to occur with corticosteroids. As a result corticosteroids should be used with caution in patients who have or may be predisposed to thromboembolic disorders.

Immunosuppressive effects/Increased susceptibility to infections
Corticosteroids can increase susceptibility to infections, mask symptoms of an infection and new infections can also appear during their use.
Corticsteroid use may cause decreased resistance as well as an inability to locate the infection.
Infections throughout the body caused by pathogens such as viruses, bacteria, fungi, protozoa or worms may be associated with the use of corticosteroids alone or in combination with other immunosuppressant agents that affect cellular immunity, humoral immunity or neutrophil function.
Such infections may be mild, but can also be serious or even fatal.
The risk infections increases with increasing corticoid doses.

People who use immunosuppressants are more susceptible to infections than healthy people. Chickenpox and measles, for example, can be serious or even fatal in non-immunised children or adults taking corticosteroids.

Administration of live or live-attenuated virus vaccines is contraindicated in patients receiving an immunosuppressive dose of corticosteroids. Dead or inactivated and biogenetically-derived vaccines may be administered to patients receiving immunosuppressive doses of corticosteroids; however, the therapeutic response to such vaccines may be diminished or they could even be ineffective.
Indicated immunisation procedures may be undertaken in patients receiving non-immunosuppressive doses of corticosteroids.

The use of methylprednisolone in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.
If corticosteroids are used in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission.

Routine use of corticosteroids in septic shock is not recommended and a systemic review concluded that short-term use of high doses of corticosteroids is not indicated. However, meta-analyses and a review of the literature suggest that longer treatment (5-11 days) with low-dose corticosteroids may decrease mortality , especially in patients suffering from septic shock and in need of vasopressor therapy.

Immune system disorders
Allergic reactions (for example, angioedema) are possible.
Since in rare cases skin reactions and anaphylactic/anaphylactoid reactions have occurred in patients receiving parenteral corticotherapy, all necessary measures should be taken before administering this product, especially if the patient has previously had an allergic reaction to a similar medicinal product.

Endocrine effects
In patients on corticosteroid therapy who are subjected to unusual stress, increased dosage of rapidly acting corticosteroids may be required before, during and after the stress situation.

The use of pharmacological doses of corticosteroids for longer periods can result in inhibition of the hypothalamic-pituitary-adrenal or HPA axis (secondary adrenal insufficiency). The degree and duration of that adrenal insufficiency varied from one patient to the next and depended on the dose, frequency and

moment of the administration and the duration of the glucocorticoid treatment. Suppression of the HPA axis can be reduced by administring the treatment every other day (see section 4.2).

In addition, abruptly stopping glucocorticoids can lead to acute adrenal insufficiency with a potentially fatal outcome.

Drug-related adrenal cortex insufficiency can be mitigated by gradual dose reduction. This type of relative insufficiency could even persist for months after the end of the treatment. The hormone therapy should be restarted in the event of any stress situation during this period.

A steroid "withdrawal syndrome", seemingly unrelated to adrenal insufficiency, can occur when therapy with glucocorticosteroids is discontinued suddenly. The symptoms of this syndrome include: anorexia, nausea, vomiting, lethargy, headache, fever, joint pain, desquamation, myalgia, weight loss and/or hypotension.
It appears that these effects are due to the sudden change in glucocorticoid concentration and not low corticosteroid levels. Since glucocorticoids can cause or worsen Cushing's syndrome, they should be avoided in patients with this type of syndrome.

An increased effect of corticosteroids has been observed in patients with hypothyroidism. The initiation of thyroid hormone replacement in patients with hyper- or hypothyroidism should be monitored during treatment with corticosteroids.

Metabolism and nutrition disorders
Corticosteroids, including methylprednisolone, can increase blood glucose levels, worsen pre-existing diabetes, and increase the risk of diabetes mellitus in patients on long-term corticosteroid therapy. This is true when the therapy is given as the main or adjuvant treatment.

Psychiatric disorders
Psychiatric disorders can occur during the use of corticosteroids. These may vary from euphoria, insomnia, moodiness, personality changes and severe depression to manifest psychotic signs. Emotional instability and existing psychotic tendencies can be aggravated by corticosteroids.

Potentially serious psychological adverse reactions may occur with systemic steroids (see section 4.8 Psychiatric disorders). The symptoms usually manifest themselves a few days to several weeks after the start of treatment. In many cases, these disorders subside when the dose is lowered or treatment is stopped. Specific treatment is sometimes necessary. Psychiatric effects have been observed after the discontinuation of corticosteroids; the frequency of this is unknown. Patients/caregivers should be encouraged to consult a physician if the patient develops psychiatric symptoms, especially if he/she appears depressed or has suicidal thoughts. Patients/caregivers should be alert to any psychiatric problems that may arise during or immediately after a gradual reduction/discontinuation of systemic steroids.

Nervous disorders
Corticosteroids should be used with caution in patients with convulsive disorders.
Corticosteroids should be used with caution in patients with myasthenia gravis (also see the description of myopathy in the section below entitled Musculoskeletal effects).
There have been reports of epidural lipomatosis in patients taking corticosteroids, generally with long-term treatment at high doses.

Visual disturbance
Corticosteroids should be used cautiously in patients with ocular herpes simplex because of the possible risk of corneal perforation. Regular ophthalmic monitoring is recommended.
Prolonged use of corticosteroids may lead to posterior subcapsular cataracts and nuclear cataracts (particularly in children), exophthalmos, or increased intraocular pressure, which may result in glaucoma with possible damage to the optic nerves.
Establishment of secondary fungal and viral infections of the eye may also be enhanced in patients receiving glucocorticoids.

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient develops symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist to assess of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.
Corticosteroid therapy has been associated with central serous chorioretinopathy, which may lead to retinal detachment.

Cardiac effects
Adverse effects of corticoids on the cardiovascular system, such as dyslipidaemia and hypertension, may predispose patients with existing cardiovascular risk factors treated long-term with high doses to additional cardiovascular adverse effects.
Corticosteroids should therefore be used wisely in these patients and careful consideration should be given to the change in risk and the need for additional cardiac monitoring. Alternate low-dose treatment may decrease the incidence of corticosteroid complications.
Systemic corticosteroids should be used with caution, and only if strictly necessary, in cases of congestive heart failure.

Vascular effects
Thrombosis including venous thromboembolism has been reported to occur with corticosteroids. As a result corticosteroids should be used with caution in patients who have or may be predisposed to thromboembolic disorders.
Corticosteroids should be used with caution in hypertensive patients.

Gastrointestinal effects
High doses of corticosteroids may produce acute pancreatitis.
There is no universal agreement on whether corticosteroids are responsible for peptic ulcers encountered during therapy. However, glucocorticoid therapy may mask the symptoms of peptic ulcer so that perforation or haemorrhage may occur without significant pain. Glucocorticoid therapy may mask peritonitis, or other signs or symptoms associated with gastrointestinal disorders, such as perforation, obstruction, or pancreatitis. The risk of the development of gastrointestinal ulcers is increased when glucocorticoids are combined with NSAIDs. In case of nonspecific ulcerative colitis glucocorticosteroids should be used with care in case there is a possibility of an imminent perforation, abscess or other pyrogenic infections. The necessary care should also be taken in cases of diverticulitis, recent intestinal anastomoses and active or latent peptic ulcer.

Hepatobiliary effects
Rarely hepatobiliary disorders were reported, in the majority of cases reversible after withdrawal of therapy. Therefore appropriate monitoring is required.

Musculoskeletal effects
Acute myopathy has been reported with the use of high doses of corticosteroids, most often in patients with disorders of neuromuscular transmission (e.g. myasthenia gravis), or in patients receiving concomitant therapy with anticholinergics, such as neuromuscular blockers (e.g. pancuronium).
This acute myopathy is generalised, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevations of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.
Osteoporosis is a common but rarely recognised undesirable effect associated with a long-term use of high doses of glucocorticosteroids. Corticosteroids should be used with caution in patients with osteoporosis.

Renal and urinary disorders
Caution is advised in patients with systemic sclerosis due to the increased incidence of scleroderma renal crisis observed with corticosteroids, including methylprednisolone.
Corticosteroids should be used with caution in patients with renal insufficiency.

Investigations

Average and high doses of hydrocortisone or cortisone can cause arterial hypertension, sodium and fluid retention and increased excretion of potassium. These effects are less common with synthetic derivatives.

Dietary measures such as salt restriction and potassium supplements may be necessary. All corticosteroids increase calcium excretion.

Corticotherapy has to be considered when interpreting a whole series of biological tests and parameters (e.g. skin tests, thyroid hormone levels).

Injury, poisoning and procedural complications
Systemic corticosteroids are not indicated and therefore should not be used to treat traumatic brain injuries. A multicentre study showed that the mortality rate was higher 2 weeks and 6 months after the trauma in patients who received methylprednisolone sodium succinate than in patients who received placebo. No causal relationship to treatment with methylprednisolone sodium succinate has been established.

Miscellaneous
Since the complications of glucocorticoid therapy depend on the dose level and duration of treatment, a benefit/risk assessment of the dose, duration of treatment and frequency of administration (daily or alternate-day administration) should be made in each individual case.

The lowest possible dose to control the condition being treated should be used and when dose reduction is possible it should be gradual.

Acetylsalicylic acid and nonsteroidal anti-inflammatory drugs should be used with caution in combination with corticosteroids.

Pheochromocytoma crisis, which can be fatal, has been reported following the administration of systemic corticosteroids. Corticosteroids should only be administered to patients with suspected pheochromocytoma or diagnosed pheochromocytoma after a careful benefit/risk assessment.

Paediatric population
Growth and development of new-borns and children on prolonged corticosteroid therapy should be carefully observed. Glucocorticosteroids may cause growth retardation in children treated long-term in daily divided doses.
This type of daily regimen is only allowed for very serious indications. Alternate-day glucocorticoid therapy usually avoids or minimises this adverse effect (see section 4.2).
Infants/toddlers and children treated long-term with corticoidsare at an increased risk of intracranial hypertension.
High doses of corticosteroids may produce pancreatitis in children.

Excipients
Methylprednisolon Eurogenerics contains lactose monohydrate and sucrose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
Methylprednisolon Eurogenerics contains sodium. This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Methylprednisolone is a cytochrome P450 enzyme (CYP) substrate and is metabolised mainly by the CYP3A4 enzyme. CYP3A4 is the dominant enzyme of the most abundant CYP subfamily in the liver of adult humans. It catalyses 6β-hydroxylation of steroids, the essential Phase I metabolic step for both endogenous and synthetic corticosteroids. Many other compounds are also substrates of CYP3A4, some of

which (like other drugs) have been shown to alter glucocorticoid metabolism by induction (upregulation) or inhibition of the CYP3A4 enzyme (**Table 1**).

CYP3A4 INHIBITORS – Drugs that inhibit CYP3A4 activity (such as ketoconazole, itraconazole, clarithromycin and grapefruit juice) generally decrease hepatic clearance and increase the plasma concentration of drugs which are a CYP3A4 substrate, such as methylprednisolone. Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic adverse effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid adverse effects, in which case patients should be monitored for systemic corticosteroid side-effects. During concomitant use of a CYP3A4 inhibitor, the dose of methylprednisolone may need to be lowered to prevent steroid toxicity (**Table 1**).

CYP3A4 INDUCERS – Drugs that induce CYP3A4 activity (such as rifampicin, carbamazepine, phenobarbital and phenytoin) generally increase hepatic clearance, resulting in decreased plasma concentration of drugs which are a CYP3A4 substrate, such as methylprednisolone. Coadministration of a CYP304 inducer may require an increase in the methylprednisolone dose to achieve the desired result (**Table 1**).

CYP3A4-SUBSTRATES – In the presence of another CYP3A4 substrate, the liver clearance of methylprednisolone may be affected, with corresponding dosage adjustments required.
It is possible that adverse events associated with the use of either drug alone may be more likely to occur with coadministration (**Table 1**).

UNDESIRABLE EFFECTS NOT CAUSED BY CYP3A4 – Other interactions and effects that occur with methylprednisolone are described in Table 1 below.

Table 1. Significant interactions/effects of drugs or substances with methylprednisolone

Drug class or type - Drug or Substance	**Interaction/Effect**
Antibiotics, Antituberculous drugs - Rifampicin	CYP3A4 INDUCER
Anticoagulants (oral)	The effect of methylprednisolone on oral anticoagulants is variable. Corticoids can both potentiate and attenuate the effects of anticoagulants when used concomitantly. As a result the degree of coagulation should be monitored to maintain the desired anticoagulant effect.
Anticonvulsants - Carbamazepine	CYP3A4 INDUCER (and SUBSTRATE)
Anticonvulsants - Barbiturates (e.g. Phenobarbital) - Phenytoin	CYP3A4 INDUCERS
Anticholinergics - Neuromuscular blockers	Corticosteroids can have an effect on the action of anticholinergics. 1) Acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blockers (for more information, see section 4.4). 2) Antagonism of the neuromuscular blocking effects of pancuronium and vecuronium has been reported in patients taking corticosteroids. This interaction could occur with any competitive neuromuscular blocker.

Antidiabetic agents - Insulin - Oral hypoglycaemic agents	Glucocorticoids may increase The need for insulin or oral hypoglycaemic agents in diabetic patients.
Antiemetics - Aprepitant - Fosaprepitant	CYP3A4 INHIBITORS (and SUBSTRATES)
Antifungals - Itraconazole - Ketoconazole	CYP3A4 INHIBITORS (and SUBSTRATES)
Antivirals - HIV-protease inhibitors	CYP3A4 INHIBITORS (and SUBSTRATES) 1) Protease inhibitors such as indinavir and ritonavir may increase plasma concentrations of corticosteroids. 2) Corticosteroids may induce the metabolism of HIV-protease inhibitors, resulting in lower plasma concentrations.
Pharmacokinetic enhancers - Cobicistat	CYP3A4 INHIBITORS Pharmacokinetic enhancers inhibit the activity of CYP3A4, resulting in decreased liver clearance and increased plasma concentrations of corticosteroids. Adjustment of the corticosteroid dose may be required (see section 4.4).
Calcium channel blockers - Diltiazem	CYP3A4 INHIBITOR (and SUBSTRATE)
Contraceptives (oral) - Ethinylestradiol/Norethindrone	CYP3A4 INHIBITOR (and SUBSTRATE)
- Grapefruit juice	CYP3A4 INHIBITOR.
Immunosuppressants - Ciclosporin	CYP3A4 INHIBITOR (and SUBSTRATE) 1) Mutual inhibition of metabolism occurs with concurrent use of ciclosporin and methylprednisolone, which may increase the plasma concentrations of either or both drugs. Therefore, it is possible that adverse events associated with the use of either drug alone may be more likely to occur with coadministration. 2) Convulsions have been reported with concurrent use of methylprednisolone and ciclosporin.
Immunosuppressants - Cyclophosphamide - Tacrolimus	CYP3A4 SUBSTRATES
Macrolide antibiotics - Clarithromycin - Erythromycin	CYP3A4 INHIBITORS (and SUBSTRATES)
Macrolide antibiotics - Troleandomycin	CYP3A4 INHIBITOR
NSAIDs (nonsteroidal anti-inflammatory drugs) - high-dose acetylsalicylic acid	1) An increased incidence of gastrointestinal bleeding and ulceration is possible during concomitant administration of corticosteroids and NSAIDs. 2) Methylprednisolone can increase the clearance of high-dose acetylsalicylic acid, which can lead to reduced serum salicylate levels. Stopping treatment with methylprednisolone can lead to elevated plasma salicylate levels and an increased risk of salicylate toxicity.
Potassium depleting agents - Thiazide diuretics	Concomitant administration of glucocorticoids and thiazide diuretics increases the risk of glucose intolerance and hypokalaemia.
Vaccines	Administration of vaccines containing live-attenuated viruses is not recommended in patients receiving immunosuppressive

	doses of corticosteroids. Inactivated and biogenetically-derived vaccines may be administered to patients receiving immunosuppressive doses of corticosteroids; however, the therapeutic response to such vaccines may be diminished or they could even be ineffective. Indicated immunisation procedures may be undertaken in patients receiving non-immunosuppressive doses of corticosteroids.
Desired interaction - tuberculosis	Methylprednisolone is administered in combination with adequate tuberculostatics in the treatment of fulminant or disseminated pulmonary tuberculosis and in the treatment of tuberculous meningitis with threatening or already established subarachnoid block.
Desired interaction - neoplastic conditions	Methylprednisolone is usually used in combination with alkylating agents, anti-metabolites and vinca alkaloids in the treatment of neoplastic conditions such as leukaemia and lymphoma.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is insufficient data on the use of methylprednisolone in pregnant women.

Corticosteroids readily cross the placenta. One retrospective study found an increased incidence of low birth weight in infants whose mothers had taken corticosteroids. In humans, the risk of low birth weight is seemingly dose-related and can be minimised by administering lower doses of corticosteroids. New-born infants whose mothers have been treated with large amounts of corticosteroids during pregnancy should be carefully observed and monitored for signs of adrenal insufficiency.

Although neonatal adrenal insufficiency is rare in infants exposed to corticosteroids *in utero*, infants exposed to substantial doses of corticosteroids should be carefully observed and monitored for signs of adrenal insufficiency.

There are no known effects on labour and delivery.

Animal studies have shown reproductive toxicity (see section 5.3).

If long-term treatment with corticoid preparations must be discontinued during pregnancy (like other chronic treatments), this treatment should be gradually discontinued (see section 4.2). However, in some cases (for example, replacement treatment for adrenal insufficiency) it may be necessary to continue treatment or even to increase the dose. In the absence of proper studies on the effects of methylprednisolone on human reproduction, this medicinal product should only be used during pregnancy after careful assessment of the benefit-risk balance for the mother and foetus.

Breastfeeding

Corticosteroids are excreted in breast milk. The corticosteroids that pass into breast milk can inhibit growth and disrupt the production of endogenous glucocorticoids in breast-fed new-borns. This medicinal product should only be used during breastfeeding after careful assessment of the benefit-risk balance for the mother and new-born/infant.

Fertility

Animal studies have shown that corticosteroids can alter fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

The effect of corticosteroids on the ability to drive and use machines has not been investigated systematically. Adverse reactions, such as dizziness, visual disturbances and fatigue, are possible after treatment with corticosteroids. In such cases, patients may not drive or use machines.

4.8 Undesirable effects

Systemic adverse reactions may be observed. Although rarely occurring in very short-term therapy, they should always be carefully traced. This is part of the follow-up of any corticotherapy, and does not specifically pertain to any particular product.
These possible adverse reactions of glucocorticoids like methylprednisolone are:

The adverse effects of methylprednisolone have been studied in the DrugDex database (Micromedex 2.0). For most adverse reactions, no information was available to determine the frequency. Some adverse effects were nevertheless classified as "common". Based on this, the adverse effects can be classified according to the following frequencies:

Table 2. Table of adverse effects

System Organ Class	Frequency	Undesirable effects
Infections and infestations	Common	Infection
	Frequency not known:	Opportunistic infection, peritonitis*
Blood and lymphatic system disorders	Frequency not known:	Leukocytosis
Immune system disorders	Frequency not known:	Drug hypersensitivity, anaphylactic reaction, anaphylactoid reaction
Endocrine disorders	Common	Cushing's syndrome, steroid withdrawal syndrome
	Frequency not known:	Hypopituitarism
Metabolism and nutrition disorders	Common	Sodium retention, fluid retention
	Frequency not known:	Hypokalaemic alkalosis, metabolic acidosis, reduced glucose tolerance, increased insulin requirement (or need for oral hypoglycaemic agents in diabetics), manifestations of latent diabetes mellitus, increased appetite (which may result in weight gain), negative nitrogen balance, dyslipidaemia, epidural lipomatosis, lipomatosis
Psychiatric disorders	Common	Affective disorder (including severe depression, euphoria),

	Frequency not known:	Psychotic disorder (including mania, delirium, hallucinations, and schizophrenia), psychotic behaviour, affective disorder (including emotional lability, drug dependence, suicidal thoughts), mental disorder, personality disorders, moodiness, confusion, abnormal behaviour, anxiety, insomnia, irritability
Nervous system disorders	Frequency not known:	Convulsions, increased intracranial pressure (with papillary oedema [benign intracranial hypertension]), amnesia, cognitive impairment, vertigo, headache
Visual disturbance	Common	Cataract
	Rare	Blurred vision (see section 4.4)
	Frequency not known:	Posterior subcapsular cataract and glaucoma, exophthalmia, chorioretinopathy
Ear and labyrinth disorders	Frequency not known:	Vertigo
Cardiac effects	Frequency not known:	Congestive heart failure (in susceptible patients), myocardial rupture following myocardial infarction, tachycardia (at high doses), bradycardia**
Vascular effects	Common	Hypertension
	Frequency not known:	Hypotension, thrombotic events
Respiratory, thoracic and mediastinal disorders	Frequency not known:	Pulmonary embolism, hiccups
Hepatobiliary effects	Frequency not known:	Hepatitis, elevated liver enzymes (e.g. SGOT, SGPT)
Gastrointestinal effects	Common	Peptic ulcer (with possible perforation and bleeding of the peptic ulcer)
	Frequency not known:	Intestinal perforation, gastric haemorrhage, pancreatitis, ulcerative oesophagitis, oesophagitis, abdominal distention, abdominal pain, diarrhoea, dyspepsia, nausea, vomiting
Skin and subcutaneous tissue disorders	Common	Skin atrophy, acne
	Frequency not known:	Erythema, angioedema, pruritus, urticaria, ecchymosis, petechiae, skin eruption, hirsutism, hyperhidrosis, skin striae

Musculoskeletal and connective tissue disorders	Common	Muscle weakness, growth retardation
	Frequency not known:	Pathologic fracture, osteonecrosis, muscle atrophy, neuropathic arthropathy, myopathy, osteoporosis, arthralgia, myalgia
Reproductive system and breast disorders	Frequency not known:	Irregular menstruation
General disorders and administration site conditions	Common	Delayed wound healing
	Frequency not known:	Fatigue, malaise, peripheral oedema
Investigations	Common	Blood potassium decreased
	Frequency not known:	Increased intraocular pressure, carbohydrate tolerance decreased, increased alanine aminotransferase, aspartate aminotransferase increased, blood alkaline phosphatase increased, urinary calcium increased, blood urea increased, suppression of reactions to skin tests
Injury, poisoning and procedural complications	Frequency not known:	Tendon rupture (especially the Achilles tendon); vertebral fractures due to prolapse

[#] Common (≥1/100, <1/10); Uncommon (≥1/1,000, <1/100); Rare (≥1/10,000, <1/1,000); Frequency not known (cannot be estimated from the available data)
* Peritonitis may be the primary sign or symptom of gastrointestinal disease such as perforation, obstruction or pancreatitis (see section 4.4).
** Following high doses

Paediatric population
The frequency, type and severity of adverse effects in children are expected to be the same as in adults.

Growth may be suppressed in case of long-term glucocorticosteroid treatment (see section 4.4).

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

Symptoms
There is no clinical syndrome of acute overdosage with methylprednisolone.
Chronic overdosage results in the typical Cushing symptoms.

Treatment
Reports of acute toxicity and/or death as a result of overdosage with corticosteroids are rare. In the event of overdosage, no specific antidote is available. Treatment should be supportive and symptomatic.
Methylprednisolone is dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: synthetic glucocorticosteroids, ATC code: H02AB04.

Glucocorticoids diffuse through the cell membranes and form complexes with specific receptors in the cytoplasma. These complexes then push into the nucleus of the cell, bind with DNA (chromatin) and stimulate the transcription of messenger RNA and the resulting protein synthesis of various enzymes ultimately responsible for the many effects observed after systemic use of glucocorticoids.

Glucocorticoids not only have an important influence on inflammatory and immune processes, but also affect carbohydrate, protein and fat metabolism. They also act on the cardiovascular system, the skeletal muscles and the central nervous system.
- Effect on the inflammatory and immune process:

The anti-inflammatory, immunosuppressive and anti-allergic properties of glucocorticoids are responsible for most of the therapeutic applications. The most important results of these properties are:
- reduction of the immunoactive cells near the inflammation focus;
- reduced vasodilation;
- stabilization of the lysosomal membranes;
- inhibition of phagocytosis;
- reduced production of prostaglandins and related substances.

A dose of 4 mg of methylprednisolone has the same glucocorticosteroid (anti-inflammatory) effect as 20 mg of hydrocortisone. Methylprednisolone has only a minimal mineralocorticoid effect (200 mg of methylprednisolone is equivalent to 1 mg of desoxycorticosterone).
- Effect on carbohydrate and protein metabolism:

Glucocorticoids have a protein catabolic action. The liberated amino acids are converted into glucose and glycogen in the liver by means of the gluconeogenesis process. Glucose absorption in peripheral tissues decreases, which can lead to hyperglycaemia and glucosuraemia, especially in patients who are prone to diabetes.
- Effect on fat metabolism:

Glucocorticoids have a lipolytic action. This lipolytic activity mainly affects the limbs. They also have a lipogenic effect which is most evident on the chest, neck and head. All this leads to a redistribution of the fat deposits.

The maximum pharmacologic activity of corticosteroids appears after the peak blood levels, suggesting that most effects of the drugs result from modification of enzyme activity rather than from direct action of the drug.

5.2 Pharmacokinetic properties

Absorption
Methylprednisolone is absorbed rapidly and the peak plasma concentration is reached approximately 1.5 to 2.3 hours after oral administration in healthy adults at all doses.

In vivo infusion into the human small intestine has demonstrated that the steroids are mainly absorbed in the proximal section of the small intestine. Absorption by the distal portion was 50% of the proximal absorption.

In man, methylprednisolone forms a weak dissociable bond with albumin and transcortin.
Approximately 40 to 90% of the drug is bound.

Distribution
Methylprednisolone is widely distributed in the tissues, crosses the blood-brain barrier and is excreted in breast milk. The volume of distribution is approximately 1.4 l/kg.

Biotransformation
Biotransformation of methylprednisolone occurs via hepatic routes qualitatively similar to that of cortisol. The major metabolites are 20 beta-hydroxymethylprednisolone and 20 beta-hydroxy-6-alpha-methylprednisone. The metabolites are mainly excreted in the urine as glucuronides, sulphates and unconjugated compounds. These conjugation reactions occur principally in the liver and to some extent in the kidney.
Like many CYP3A4 substrates, methylprednisolone can also be a substrate for P-glycoprotein, a transporter of the ATP-Binding Cassette (ABC) family, which can affect tissue distribution and interactions with other drugs.

Elimination
The mean elimination half-life of total methylprednisolone is between 1.8 and 5.2 hours and the total clearance is around 5 to 6 ml/min/kg.

Special populations

Sex
The clearance of methylprednisolone following a single dose intravenous administration was higher in healthy women than in healthy men: 0.45 versus 0.29 l/h/kg. Nevertheless, there were no differences in the pharmacodynamic measurements.

Elderly patients
The clearance of methylprednisolone following a single dose intravenous administration was lower in healthy elderly men (69 to 82 years) than in healthy young men (24 to 37 years): 0.24 versus 0.36 l/h/kg.

Paediatric population
The clearance of methylprednisolone is mildly age-related. Younger patients seem to metabolise methylprednisolone faster. In a study of intravenous single-dose administration in 14 patients with nephrotic syndrome, the younger patients (< 13 years) manifested higher clearance than the older patients (> 13 years): 0.53 versus 0.38 l/h/kg.

Renal insufficiency
In a study of intravenous single-dose administration in six male patients with chronic renal insufficiency, the pharmacokinetics of methylprednisolone, with a mean clearance of 0.28 l/h/kg, were unchanged versus the healthy subjects. In addition, there were no differences in the pharmacodynamic measurements in patients with chronic renal insufficiency.

Hepatic insufficiency
In a study of an intravenous single-dose administration in six male patients with chronic liver disease, the pharmacokinetics of methylprednisolone, with a mean clearance of 0.29 l/h/kg, were similar to those in the healthy subjects.

5.3 Preclinical safety data

Non-clinical data do not indicate any particular risk for humans. These data are derived from conventional studies of safety pharmacology and repeated dose toxicity.
The observed toxicity in the repeated dose studies refers to the expected toxicity at persistent exposure to exogenous adrenal steroids.

Carcinogenicity
Methylprednisolone has not been formally evaluated in carcinogenicity studies in rodents. Tests have been performed with other glucocorticoids to test carcinogenicity in mice and rats, with variable results. However, the published data indicate that several similar glucocorticoids such as budesonide, prednisolone and triamcinolone acetonide may increase the incidence of hepatocellular adenomas and carcinomas after oral administration in drinking water in male rats. Such carcinogenic effects occurred at doses lower than the clinically accepted doses expressed in mg/m^2.

Genotoxicity
Limited studies of bacterial and mammalian cells have shown no potential for gene or chromosome mutations.

Reproductive toxicity
Corticosteroids administered to rats have been shown to reduce fertility. In rats, corticosteroids induce a reduction in the ovules, a decrease in the number of implantations and the number of live foetuses.

Corticosteroids are teratogenic in many animal species after doses equal to doses used in humans. In animal reproductive studies, glucocorticoids such as methylprednisolone have been shown to cause an increase in the incidence of malformations (cleft palate, skeletal malformations), embryo-foetal lethality (such as an increase in resorptions) and intrauterine growth inhibition.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Sucrose
Sodium starch glycolate (Type A)
Silica, colloidal anhydrous (E551)
Magnesium stearate (E572)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blisters: 3 years.
Bottles: 2 years.

6.4 Special precautions for storage

Blister packs: This medicinal product does not require any special storage conditions.
Bottles: Do not store above 30°C.
After first opening (bottles): Do not store above 30°C.

6.5 Nature and contents of container

Methylprednisolon Eurogenerics tablets are packed in Al/PVC/PCTFE blisters and white HPDE bottles with polypropylene (PP) cap.

Methylprednisolon Eurogenerics 4 mg tablets are available in in blister packs containing 20, 30 or 100 tablets and bottles containing 20, 30 or 100 tablets.
Methylprednisolon Eurogenerics 16 mg tablets are available in blister packs containing 20, 30, 50 or 100 tablets and bottles containing 20, 50, 100 tablets .

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

EG (Eurogenerics) NV
Heizel Esplanade b22
1020 Brussel
België

8. MARKETING AUTHORISATION NUMBER(S)

Methylprednisolon Eurogenerics 4 mg tabletten:	RVG 116593
Methylprednisolon Eurogenerics 16 mg tabletten:	RVG 116594

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21 maart 2016
Date of latest renewal: 27 februari 2021

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft rubriek 4.8: 27 april 2021.