MEDROL 4 mg, tablet
MEDROL 16 mg, tablet

Méthylprednisolone

Date: January 2021. Version n° 08

Reference market: France

West Africa

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MEDROL 4 mg, tablet

MEDROL 16 mg, tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

MEDROL 4 mg

Méthylprednisolone.....4,0 mg

For one tablet

MEDROL 16mg

Methylprednisolone
..... 16 mg

For one tablet.

Excipients with known effect: lactose, sucrose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

tablet.

MEDROL 4mg

White, elliptical shaped tablet, with a groove in the shape of a cross on one side and the inscription "MEDROL 4" on the other side. The score line is not intended to be used to divide the tablet.

MEDROL 16MG

WHITE ELLIPTICAL, CONVEX TABLET MARKED "MEDROL 16" ENGRAVED ON ONE SIDE AND AN CROSS ENGRAVING ON THE OTHER SIDE. THE SCORE LINE IS NOT INTENDED TO BE USED TO DIVIDE THE TABLET.4. CLINICAL PARTICULARS

4.1. Therapeutic indications

DISORDERS OR DISEASES:

- COLLAGENOSIS, CONNECTIVE TISSUE DISEASES
  - Systemic diseases characterised by progressive flare-ups, notably: disseminated lupus erythematosus, vasculitis, polymyositis, sarcoidosis.
- DERMATOLOGICAL
  - Severe autoimmune bullous dermatosis, in particular pemphigus and bullous pemphigoid.
  - Serious forms of infant angiomas.
  - Certain forms of lichen planus.
  - Certain acute urticaria.
  - Serious forms of neutrophilic dermatosis.
- DIGESTIVE
  - Progressive flare-ups of haemorrhagic rectocolitis and Crohn's disease.
  - Active autoimmune chronic hepatitis (with or without cirrhosis).
  - Severe acute alcoholic hepatitis, histologically proven.
- ENDOCRINE
  - Subacute severe de Quervain's thyroiditis.
  - Certain hypercalcaemias.
- HAEMATOLOGICAL

- Severe immune thrombocytopoenic purpura.
- Autoimmune haemolytic anaemias.
- Combined with various chemotherapies in the treatment of malignant lymphoid haemopathies.
- Chronic acquired or congenital erythroblastopoenia.

- INFECTIONS
  - Tuberculous pericarditis and serious, life-threatening forms of tuberculosis.
  - Pneumocystis carinii pneumopathy with severe hypoxia.
- NEOPLASTIC
  - Antiemetic treatment during antineoplastic chemotherapy.
  - Oedematous and inflammatory flare-up associated with antineoplastic treatment (radiation and chemotherapy).
- NEPHROLOGICAL
  - Nephrotic syndrome with minimal glomerular lesions.
  - Nephrotic syndrome of primary segmental and focal hyalinosis.
  - Lupus nephropathy stages III and IV.
  - Intrarenal granulomatous sarcoidosis.
  - Vasculitis affecting the kidneys.
  - Primitive extra-capillary glomerulonephritis.
- NEUROLOGICAL
  - Myasthaenia.
  - Cerebral oedema caused by tumour.
  - Chronic, idiopathic, inflammatory polyradiculoneuritis.
  - Infantile spasms (West syndrome) / Lennox-Gastaut syndrome.
  - Multiple sclerosis flare-up, following intravenous corticotherapy.
- OPHTHALMOLOGICAL
  - Severe anterior and posterior uveitis.
  - Oedematous exophthalmos.
  - Certain optic neuropathies, following intravenous corticotherapy (in this indication, first-line oral therapy is ill-advised).
- ENT
  - Certain serious types of otitis.
  - Nasosinus polyposis.
  - Certain acute or chronic types of sinusitis.
  - Seasonal allergic rhinitis, short term.
  - Acute laryngismus stridulus (subglottic laryngitis) in children.
- RESPIRATORY
  - Persistent asthma, preferably short term, in the event of strong dose inhaler treatment failure.
  - Exacerbations of asthma, in particular acute severe asthma.
  - Chronic, obstructive pulmonary disease when the reversibility of the obstructive syndrome is being assessed.
  - Progressive sarcoidosis.
  - Widespread interstitial pulmonary fibrosis.
- RHEUMATOLOGICAL
  - Rheumatoid arthritis and certain types of polyarthritis.
  - Rhizomelic pseudo-polyarthritis and Horton’s disease.
  - Acute articular rheumatism.
  - Severe and uncontrolled cervicobrachial neuralgia.
- ORGAN AND ALLOGENEIC HAEMATOPIETIC STEM CELL TRANSPLANT
  - Prophylaxis or graft reject treatment.
  - Prophylaxis or graft-versus-host reaction treatment.

4.2. Posology and method of administration

Posology

Oral use.

Anti-inflammatory equivalence (equipotential) per 5 mg of prednisone: 4 mg of methylprednisolone.

Swallow the tablets with a little water during meals.

ONLY FOR ADULTS AND CHILDREN OVER 6 YEARS OLD.

MEDROL 4 mg is especially suited to treatments requiring low doses.

MEDROL 16 mg is especially suited to initial or short-term therapy requiring moderate to strong doses.

There are more appropriate doses for maintenance therapy.

There are more suitable pharmaceutical forms for children under 6 years old.

Adults

The dose varies depending on the diagnosis, severity of the disorder, prognosis, patient response and tolerance to treatment.

MEDROL 4mg

Initial treatment: 0.3 mg - 1.0 mg/kg/day of methylprednisolone (meaning 0.35 mg to 1.2 mg/kg/day of prednisone equivalent). For informational purposes: 4 to 14 tablets for a 60 kg adult.

During serious inflammatory diseases, the dosage varies from 0.60 to 1.00 mg/kg/day methylprednisolone (= 0.75 mg/kg/day to 1.2 mg/kg/day prednisone equivalent). For informational purposes: 9 to 14 tablets per day for a 60 kg adult.

Highly exceptional situations may require higher doses.

Maintenance treatment: from 4 - 12 mg/day of methylprednisolone, meaning 1 - 3 tablets per day.

MEDROL 16mg

The dose varies depending on the diagnosis, severity of the disorder, prognosis, patient response and tolerance to treatment.

Initial treatment: 0.3 mg - 1.0 mg/kg/day of methylprednisolone (meaning 0.35 mg to 1.2 mg/kg/day of prednisone equivalent). For informational purposes: 1 - 4 tablets for a 60 kg adult.

During serious inflammatory diseases, the dosage varies from 0.60 - 1.00 mg/kg/day of methylprednisolone (meaning 0.75 mg/kg/day prednisone equivalent). For informational purposes: 2 - 4 tablets per day for a 60 kg adult.

Highly exceptional situations may require higher doses.

Children over 6 years old (due to the pharmaceutical form)

The dosage must be adjusted to the disease and weight of the child.

MEDROL 4mg

Initial treatment: 0.4 mg to 1.6 mg/kg/day methylprednisolone (= 0.5 mg to 2 mg/kg/day prednisone equivalent). For informational purposes: 2.5 to 10 tablets for a 25 kg child.

Maintenance treatment: 0.2 mg - 0.4 mg/kg/day of methylprednisolone (meaning 0.25 mg to 0.5 mg/kg/day of prednisone equivalent). For informational purposes: 1 - 2.5 tablets for a 25 kg child.

MEDROL 16mg

Initial treatment: 0.4 mg - 1.6 mg/kg/day of methylprednisolone (meaning 0.5 mg to 2 mg/kg/day of prednisone equivalent). For informational purposes: 1 to 4 tablets for a 40 kg child.

MEDROL tablets at a lower dosage (4 mg) are available and should be used if necessary, to achieve the appropriate dosage.

Corticotherapy on alternating days (one day without the corticoid and the next day with a double dose of the daily dose required) can be prescribed to children to attempt to limit growth delays. This alternating day regimen can only be contemplated after checking the inflammatory disease with strong doses of corticoids, and if no rebound was observed during the reduction.

In general

Treatment at the “loading dose” must be continued until the disease has been durably controlled. Reduction must be slow. The goal is to wean the patient. Continuing a maintenance dose (minimum effective dose) is sometimes necessary.

For prolonged treatment at high doses, the initial doses can be split into two daily doses. Thereafter, the daily dose can be administered in a single dose, preferably in the morning with breakfast.

Discontinuing treatment

The weaning pace depends mainly on the duration of treatment, the starting dose and the disease.

Treatment involves a resting period for ACTH and cortisol secretions, at times with long-lasting adrenal impairment. During weaning, discontinuation must be done gradually, in increments due to the risk of a relapse: on average a 10% reduction every 8 - 15 days.

Discontinuing treatment gradually is not necessary for short treatments under 10 days.

During dose reduction (prolonged treatment): at dosages of 5 - 7 mg of prednisone equivalent when the original illness no longer requires corticotherapy, it is recommended to replace the synthetic corticoid with 20 mg/day of hydrocortisone until corticotropic function resumes. If corticotherapy must be continued at a dose of less than 5 mg prednisone equivalent per day, it is possible to add a small dose of hydrocortisone to reach a hydrocortisone equivalent of 20 - 30 mg per day. If the patient is only on hydrocortisone, it is possible to test the corticotrope axis using endocrine tests. These tests do not independently eliminate the possibility of adrenal impairment due to stress.

Whilst on hydrocortisone or even well after stopping, the patient must be warned of the need to increase the usual dosage or to resume replacement therapy (e.g. 100 mg of intramuscular hydrocortisone every 6 - 8 hours) in case of stress: surgery, trauma, infection.

4.3. Contraindications

This medicine is generally contraindicated in the following situations: (however, there are no absolute contraindications for corticotherapy for a vital indication).

- All infectious conditions, except for specific indications (see section 4.1) not controlled by a specific treatment.
- Certain progressive viruses (especially hepatitis, herpes, chickenpox, herpes zoster),
- Psychotic conditions still uncontrolled with treatment,
- Live or live attenuated vaccines (for yellow fever, tuberculosis, rotavirus, measles, mumps, rubella, chickenpox, herpes zoster, flu) in patients receiving doses of dosages above 10 mg/d of equivalent-prednisone (or > 2 mg/kg/d in children or > 20 mg/d in children over 10 kg) for more than two weeks and for the "bolus" of corticosteroids (with the exception of inhaled and local routes), and for the 3 months after discontinuing the corticosteroid: risk of generalised, possibly fatal, vaccine disease,
- Hypersensitivity to the active substance or to one of the excipients listed in section 6.1.

This medicine is not usually recommended concomitantly with acetylsalicylic acid at anti-inflammatory doses, with mifamurtide or with a potent CYP3A4 inhibitor (see section 4.5).

4.4. Special warnings and precautions for use

Special warnings

In case of gastro-duodenal ulcer, corticotherapy is not contraindicated if combined with an anti-ulcer treatment. Where there is a history of ulcer, corticotherapy may be prescribed with clinical monitoring, after an endoscopy if required.

Immunosuppressive effects/increased susceptibility to infection

Corticotherapy may promote the occurrence of various infectious complications notably due to bacteria, yeasts and parasites. The onset of malignant strongyloidiasis is a significant risk. All patients coming from an endemic zone (tropical, subtropical and southern European regions) must undergo testing for parasites in stools and a systematic eradication treatment before corticotherapy.

Active signs of infection can be masked by corticotherapy.

The administration of live or live attenuated vaccines is contraindicated in patients receiving dosages above 10 mg/d of equivalent-prednisone (or > 2 mg/kg/d in children or > 20 mg/d in children over 10 kg) for more than two weeks and for the "bolus" of corticosteroids (with the exception of inhaled and local routes), and for the 3 months after discontinuing the corticosteroid therapy (see sections 4.3 and 4.5). Non-live or inactivated live vaccines can be administered to patients receiving immunosuppressive doses of corticosteroids. However, the response to these vaccines may be reduced. The immunisation procedures indicated can be conducted in patients receiving non-immunosuppressive doses of corticosteroids.

Before commencing treatment, it is important to rule out any possibility of a visceral focus, especially tuberculous, and to monitor for the appearance of infectious pathologies during treatment.

In case of earlier tuberculoses, a prophylactic anti-tuberculosis treatment is required if there are considerable radiological sequelae and if it cannot be confirmed that a well-conducted, six-month treatment with rifampicin has been given.

Subjects treated with immunosuppressants are more susceptible to infections than healthy subjects.

The role of corticosteroids in septic shock is controversial, with early studies reporting beneficial and detrimental effects. More recently, studies have indicated that a complementary treatment with corticosteroids may be beneficial to patients with established septic shock and adrenal insufficiency. However, their routine use in the event of septic shock is not recommended and a systematic review has concluded that the use of high-dose corticosteroids for a short period is not recommended. However, meta-analyses and another review suggest that longer courses (5-11 days) of low-dose corticosteroids might reduce mortality, especially in cases of septic shock requiring vasopressor treatment.

Immune system

Allergic reactions (Quincke’s oedema) may occur.

Rare cases of skin reactions and anaphylactic/anaphylactoid reactions have been observed in patients receiving treatment with corticosteroids. It is therefore appropriate to take the necessary precautionary measures before treatment, especially if the patient has a history of allergy to a medicine.

This medicinal product contains lactose produced from cow’s milk. This medicinal product should be used with caution in patients with known or suspected hypersensitivity to cow’s milk or its component or other dairy products, as it may contain traces of dairy ingredients.

Endocrine function

In patients on corticosteroids who are subject to an unusually stressful event, the increase in the dose of rapid-action corticosteroids is indicated before, during and after the stressful event.

Pharmacologic doses of corticosteroids administered for prolonged periods may result in hypothalamic-pituitary-adrenal inhibition (secondary adrenocortical insufficiency). The extent and duration of the adrenocortical insufficiency produced varies from one patient to another and depends on the dose, frequency, time of administration and duration of treatment with glucocorticoids. This effect can be minimised by administering the treatment every two days (see section 4.2, Posology and method of administration, Administration every two days.)

In addition, the sudden discontinuation of corticosteroids may cause acute adrenal insufficiency, which can be fatal.

A steroid-linked “withdrawal syndrome”, visibly unrelated to adrenocortical insufficiency, may also occur following abrupt discontinuation of glucocorticoids. This syndrome includes symptoms such as: anorexia, nausea, vomiting, lethargy, headache, fever, joint pain, peeling of the skin, myalgia, weight loss, and/or hypotension. It would seem that these effects are due to the sudden change in the concentration of glucocorticoids, rather than low levels of corticosteroids.

Considering that glucocorticoids may result in or aggravate Cushingoid disorders, the use of glucocorticoids should be avoided in patients with Cushing’s disease.

Metabolism and nutrition

Corticosteroids, including methylprednisolone, can increase blood glucose, aggravate pre-existing diabetes mellitus or predispose patients who receive them long term to diabetes.

Psychiatric effects

Mental disorders can occur during the use of corticosteroids, such as euphoria, insomnia, mood swings, personality changes , severe depression and also serious psychotic events. In addition, existing emotional instability, or psychotic tendencies can be aggravated by corticosteroids.

Potentially severe adverse psychiatric reactions can occur with systemic steroids (see section 4.8, Adverse effects, Psychiatric disorders).

These symptoms typically emerge within a few days or weeks of starting treatment. Although a specific treatment can in some cases be necessary, most of these reactions disappear after reducing the dose or discontinuing treatment. Psychological effects have been reported upon withdrawal of corticosteroids; their frequency is unknown. Patients/caregivers should be asked to seek a medical opinion if psychological symptoms develop in the patient, especially if depression or suicidal ideation is suspected. Patients/caregivers must be alerted to the possible onset of psychiatric disorders that can occur during or immediately after reducing the dose or discontinuing systemic steroids.

Nervous system

Corticosteroids should be used with caution in patients with convulsive disorders.

Corticosteroids should be used with caution in patients with myasthenia gravis (see the paragraph on myopathy in the section Musculoskeletal effects).

Although controlled clinical trials have shown the efficacy of glucocorticoids in accelerating the resolution of acute attacks of multiple sclerosis, they do not show that corticosteroids affect the final outcome or natural evolution of this disease. The studies indicate that relatively high doses of corticosteroids are required to demonstrate a significant effect (see section 4.2).

Cases of epidural lipomatosis have been reported in patients treated with corticosteroid therapy, usually when used at high doses in the long term.

Ocular system

The prolonged use of corticosteroids may cause subcapsular cataracts and nuclear cataracts (especially in children), exophthalmia or an increase in intra-ocular pressure, which may lead to glaucoma, possibly affecting the optic nerves.

The occurrence of secondary fungal and viral eye infections may also increase in patients taking glucocorticoids.

Corticosteroid treatment has been associated with central serous chorio-retinopathy, which may result in retinal detachment.**Vision disorders**

Visual disturbances may occur during treatment with systemic or topical corticosteroids. In case of blurred vision or any other visual symptom appearing during treatment with a corticosteroid, an ophthalmological examination is required, in particular for cataracts, glaucoma, or rarer lesions such as central serous chorio-retinopathy, described with both systemic and topical administration of corticosteroids.

Cardiac system

The adverse effects of glucocorticoids on the cardiovascular system, such as dyslipidaemia and hypertension, may predispose treated patients with existing cardiovascular risk factors to other cardiovascular effects in cases of prolonged use at high doses. Accordingly, corticosteroids should be used with caution in these patients, attention should be paid to the changing risks and additional heart monitoring should be provided, if necessary. Treatment at low doses or every two days may reduce the incidence of complications of corticosteroid therapy.

In the case of congestive heart failure, systemic corticosteroids should be used with caution, and only if strictly necessary.

Vascular system

Thromboses, including cases of venous thromboembolic disease, have been reported with corticosteroids. Accordingly, corticosteroids should be used with caution in patients who have or who may be predisposed to thromboembolic disorders.

In case of hypertension, corticosteroids should be used with caution.

Gastrointestinal system

High doses of corticosteroids may cause acute pancreatitis

The use of corticoids requires specially adapted monitoring, especially in the elderly and in the case of ulcerative colitis (risk of perforation), recent intestinal anastomosis, renal failure, liver failure.

Corticosteroid therapy can hide peritonitis or other signs, or symptoms associated with gastrointestinal disorders such as perforation, an obstruction or pancreatitis.

The risk of developing gastrointestinal ulcers increases in the event of combination with nonsteroidal anti-inflammatories.

Hepatobiliary effects

Hepatobiliary disorders have been reported rarely and were reversible in the majority of cases when treatment was stopped. Adequate monitoring is therefore required.

Musculoskeletal effects

Acute myopathy has been reported during the use of high doses of corticosteroids, most often occurring in patients with neuromuscular transmission disorders (e.g. myasthenia gravis), or in patients receiving concomitant treatment with anticholinergics, such as neuromuscular inhibitors (e.g. pancuronium). This acute myopathy is generalised, may involve the ocular and respiratory muscles, and may result in quadriparesis. We can observe an increase in creatine

kinase. Clinical improvement or recovery, after discontinuing the corticosteroids, may take several weeks to several years.

The use of corticosteroids requires monitoring in case of osteoporosis and myasthenia gravis.

Renal and urinary disorders

Caution is required in patients with systemic sclerosis, as an increase in the incidence of scleroderma renal crises has been observed with corticosteroids, including methylprednisolone. Blood pressure and renal function (creatinine S) should therefore be checked regularly. In case of suspicion of renal crisis, blood pressure must be monitored closely.

Corticosteroids should be used with caution in patients with renal impairment.

Use in children

The growth and development of infants and children should be carefully noted following prolonged treatment with corticosteroids.

Infants and children receiving prolonged corticosteroid therapy are particularly at risk of intracranial hypertension.

High doses of corticosteroids may cause pancreatitis in children.

Others

Acetylsalicylic acid (aspirin) and nonsteroidal anti-inflammatories should be used with caution concomitantly with corticosteroids.

Pheochromocytoma crisis, which can be fatal, has been reported after the administration of corticosteroids by systemic route. Corticosteroids should only be administered to patients with suspected or demonstrated pheochromocytoma after an appropriate risk/benefit assessment.

It is expected that the concomitant administration of CYP3A inhibitors, including products containing cobicistat, increases the risk of systemic side effects. The combination should be avoided, unless the benefits are greater than the increased risk of systemic side effects of corticosteroids; in this case, patients should be monitored to detect any systemic side effects of the corticosteroids (see section 4.5)

This medicinal product contains lactose. Patients with galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption syndrome (rare hereditary diseases) should not take this medicinal product.

This medicinal product contains sucrose.

Patients with fructose intolerance, glucose-galactose malabsorption syndrome, or sucrase/isomaltase deficiency (rare hereditary diseases) should not take this medicine.

Athletes must be warned, because this preparation contains an active ingredient that can induce a positive result in doping tests. Precautions for use

Long-term corticoid treatment

Diets low in rapidly absorbed sugars and high in protein must be combined due to the hyperglycaemic and protein catabolic effect with a negative nitrogen balance.

Fluid retention is common, a possible contributor to an elevation in blood pressure. Sodium intake must be reduced for daily dosages over 15 or 20 mg prednisone equivalent and moderated in long-term low-dose treatment. Potassium supplements are justified only in case of high doses prescribed over the long term or in case of risk of cardiac rhythm disorders or in combination with hypokalaemia treatments.

The patient must systematically take calcium and vitamin D.

When corticotherapy is necessary, diabetes is not a contraindication, but the treatment can cause an imbalance. It is appropriate to reassess the care offered to patients.

Oral or injectable corticoids can promote the onset of tendinopathy and even tendon ruptures (rare). This risk increases if co-prescribed with fluoroquinolones and in dialysis patients with secondary hyperparathyroidism or who have undergone a renal transplant.

Corticosteroids by systemic route are not indicated in the treatment of cranial trauma and should therefore not be used in these cases. A multi-centre study has shown an increase of mortality two weeks and after six months after a cranial trauma in patients receiving methylprednisolone hemisuccinate compared to the placebo group. A causal relationship with methylprednisolone hemisuccinate has not been established.

In the case of a long treatment course with corticosteroids, the patient will be monitored clinically and biologically to look for any complications.

Patients must avoid contact with people who have chickenpox or measles. These viruses may follow a more severe, or even fatal development in unimmunised children or adults taking corticosteroids.

Thrombosis, including venous thromboembolic events, have been reported with the use of corticosteroids. Corticosteroids should therefore be used with caution in patients with thromboembolic disorders, or who may be predisposed to such disorders.

A precaution is to be taken in case of combination with topical gastrointestinal, antacids and adsorbent products.

Discontinuing treatment

The pace of weaning principally depends on the duration of treatment, the starting dose and the disease.
Treatment involves a resting period for ACTH and cortisol secretions, at times with long-lasting adrenal impairment.

During the weaning period (except for short treatments of less than 10 days), discontinuation must be progressive and incremental due to the risk of relapse: on average a 10% reduction every 8 to 15 days.

At dosages of 5 - 7 mg of prednisone equivalent when the original illness no longer requires corticotherapy, it is recommended to replace the synthetic corticoid with 20 mg/day of hydrocortisone until corticotropic function resumes.

4.5. Interaction with other medicinal products and other forms of interaction

HYPOKALAEMICS

Hypokalaemia is a predisposing factor for heart rhythm disorders (torsades de pointes, in particular), and increases the toxicity of certain medicinal products such as digoxin. For this reason, hypokalaemia-inducing medicinal products are involved in a large number of interactions. These include hypokalaemia diuretics, alone or combined, stimulant laxatives, glucocorticoids, tetracosactide and amphotericin B (IV route).

METABOLISM BY CYP3A4

Methylprednisolone is a substrate of cytochrome P450 enzymes (CYP) and is primarily metabolised by the enzyme CYP3A4. CYP3A4 is the dominant enzyme of the most abundant CYP subfamily in the liver of adult subjects. It catalyses the 6β-hydroxylation of steroids, the essential step in the phase I metabolism of the endogenous corticosteroids or synthesis.

Many other compounds are also substrates of CYP3A4, some, of which (as well as other medicinal products) have been shown to alter glucocorticoid metabolism by induction or inhibiting this enzyme.

+ CYP3A4 inhibitors: [Antibiotics (isoniazid), an antiemetic (aprepitant, fosaprepitant), antifungals (itraconazole, ketoconazole), antivirals (HIV protease inhibitors: indinavir, ritonavir), pharmacokinetic boosting agents (cobicistat) used in the treatment of HIV, calcium antagonists (diltiazem), oral contraceptives (ethinyl estradiol, norethindrone), grapefruit juice,

immunosuppressants (cyclosporin), macrolide antibiotics (clarithromycin, erythromycin, troleandomycin)]**:**

Medicines that inhibit the activity of CYP3A4 generally decrease hepatic clearance and increase the plasma concentration of medicines that are substrates of this enzyme such as methylprednisolone. In the case of concomitant treatment with a CYP3A4 inhibitor, it is necessary to adjust the dose of methylprednisolone to prevent corticosteroid toxicity manifestations.

+ CYP3A4 inducers: [Antibiotics, anti-TB drugs (rifampin), anticonvulsants (carbamazepine, phenobarbital, and phenytoin)]:

Medicines that induce the activity of CYP3A4 generally increase hepatic clearance and decrease the plasma concentration of medicines that are substrates of this enzyme. In the case of concomitant administration, an increase in the dose of methylprednisolone may be necessary to achieve the desired result.

+ CYP3A4 substrates: [Anticonvulsants (carbamazepine), antiemetics (aprepitant, fosaprepitant), antifungals (itraconazole, ketoconazole), antivirals (HIV protease inhibitors: indinavir, ritonavir), calcium antagonists (diltiazem), oral contraceptives (ethinylestradiol/norethindrone), immunosuppressants (cyclosporin, cyclophosphamide, tacrolimus), macrolide antibiotics (clarithromycin, erythromycin)]:

In the presence of another CYP3A4 substrate, the hepatic clearance of methylprednisolone may be affected, which requires a corresponding adaptation of the dose. Concomitant administration could increase the likelihood of adverse effects associated with one or other medicine administered alone.

Contraindicated combinations

+ Live attenuated vaccines (for yellow fever, tuberculosis, rotavirus, measles, mumps, rubella, chickenpox, herpes zoster, flu)

In patients receiving doses of dosages above 10 mg/d of equivalent-prednisone (or > 2 mg/kg/d in children or > 20 mg/d in children over 10 kg) for more than two weeks and for the "bolus" of corticosteroids (with the exception of inhaled and local routes), and for the 3 months after discontinuing the corticosteroid: risk of generalised, possibly fatal, vaccine disease,

Inadvisable combinations

+ Anti-inflammatory doses of acetylsalicylic acid ≥ 1 g per dose and/or ≥ 3 g per day

Increased risk of bleeding.

Moreover, methylprednisolone may increase the clearance of acetylsalicylic acid administered at high doses, which may cause a reduction in serum salicylate concentrations. Discontinuation of methylprednisolone treatment may cause an increase in serum salicylate concentrations and may cause increased risk of salicylate toxicity. **+ Mifamurtide**

Risk of a decrease in efficacy of mifamurtide.

+ Potent CYP34A inhibitors

In case of prolonged use by oral or inhalation routes: increase in plasma concentrations of the corticosteroid caused by a decrease in its hepatic metabolism due to the inhibitor, with the risk of Cushing's syndrome, even adrenal insufficiency. Favour an unmetabolized corticosteroid.

Combinations subject to precautions for use

+ Medicinal products that can cause torsades de pointes:

Increased risk of ventricular rhythm disorders, in particular torsades de pointes.

Correct any hypokalaemia before administering the product and perform clinical, electrolyte and ECG monitoring.

+ Oral anticoagulants (acenocoumarol, apixaban, dabigatran, fluindione, phenindione, rivaroxaban, warfarin)

Glucocorticoids (systemic and rectal routes): possible corticotherapy impact on the metabolism of vitamin K antagonist and on coagulation factors. Risk of haemorrhaging linked to high dose corticotherapy (digestive mucosa, vascular fragility) or to treatment lasting longer than 10 days.

When the combination is justified, increase monitoring: where appropriate, biological check on the 8th day with vitamin K antagonists, then every 15 days during the corticotherapy and after it has been discontinued.

+ Vitamin K antagonists (acenocoumarol, fluindione, warfarin)

For doses between 0.5 and 1 g of methylprednisolone administered in bolus: increased effect of the antivitamin K and risk of bleeding.

Check INR 2 to 4 days after the methylprednisolone bolus or with any signs of bleeding.

+ Other potassium-lowering

Increased risk of hypokalaemia.

Monitoring of kalaemia with correction, if needed.

Potassium monitoring and correction, if needed.

+ Digitalis (Digoxin)

Hypokalaemia increases the toxic effects of digitalis.

Correct any hypokalaemia beforehand and monitor clinical signs, electrolytes and ECG.

+ Enzyme inducers

Decrease in plasma concentrations and the efficacy of corticosteroids caused by an increase in their hepatic metabolism due to the inducer: the consequences are particularly severe in patients with Addison's disease treated with hydrocortisone and in cases of transplant.

Clinical and biological monitoring; corticosteroid dose adjustment during treatment by inducer and after its discontinuation.

+ Anticonvulsant enzyme inducers (carbamazepine, phenobarbital, phenytoin, primidone, fosphenytoin)

Decrease in plasma concentrations and the efficacy of corticoids due to their increased liver metabolism by the inducer: the consequences are particularly severe in addisonian and transplant patients treated with hydrocortisone.

Clinical and biological monitoring; corticoid dosage adjustment during induction treatment and after stopping it.+ Antidiabetic medicines

Increase in glycaemia with occasional ketoacidosis caused by decreased carbohydrate tolerance due to corticoids.

Warn the patient and reinforce glycaemia and urine self-monitoring, especially when initiating treatment. The dosage of diabetes treatment might need to be adjusted during and after corticoid treatment.

+ Isoniazid

Described for prednisolone: decreased plasma concentrations of isoniazid. Mechanism invoked: increase in the hepatic metabolism of isoniazid, potentially by acetylation, and decrease in that of glucocorticoids and potential effect on isoniazid clearance.

Clinical and biological monitoring.**+ Gastrointestinal topics, antacids and adsorbent products**

Decrease in the absorption of methylprednisolone. As a precaution, topical gastrointestinal products and antacids should be taken at a separate time from this medicinal product (more than 2 hours apart, if possible).

+ Cobimetinib

Increased risk of bleeding.Clinical monitoring.

Combinations to be used with caution

+ Analgesic doses of acetylsalicylic acid or antipyretics ≥ 500 mg per dose and/or < 3 g per day

Increased risk of bleeding.

+ Non-steroidal anti-inflammatories

Increased risk of ulceration and gastrointestinal bleeding.

+ Antihypertensives

Decreased antihypertensive effect (water retention due to corticosteroids).

+ Alpha interferon

Risk of inhibition of interferon action.

+ Fluoroquinolones

Possible increased risk of tendinopathy, even tendon rupture (rare), particularly in patients receiving prolonged corticotherapy.

+ Non-depolarising curares

With IV glucocorticoids: risk of severe myopathy, which is reversible after a potentially long period of time (several months) (see section 4.4).

Antagonism of the neuromuscular blocking effects of pancuronium and vecuronium has been described in patients receiving corticosteroids. This interaction can be expected with all competing curariform agents.

+ Aromatase inhibitor (aminoglutethimide)

The adrenal function induced by aminoglutethimide may exacerbate the endocrine changes caused by prolonged treatment with glucocorticoids.

+ Anticholinesterases

Steroids can reduce the effects of anticholinesterases on myasthenia gravis.

+ Antivirals (HIV protease inhibitors)

Corticosteroids may have an inductive effect on the metabolism of HIV protease inhibitors and thus reduces their plasma concentrations.

+ Potent CYP3 inhibitors

In case of prolonged use by oral or inhaled route, increase in the plasma concentrations of the corticoid by decreasing its hepatic metabolism by the inhibitor, with the risk of the emergence of a Cushingoid syndrome.

+ Heparin

Increased risk of bleeding.

4.6. Fertility, pregnancy and breastfeeding

Pregnancy

In animals, experimentation highlights a teratogenic effect of corticosteroids when they are administered in females at high doses.

However, corticosteroids do not appear to cause congenital anomalies when they are administered to pregnant women.

Given that no adequate human reproduction study has been conducted with methylprednisolone, this medicine will only be used during pregnancy after a thorough assessment of the benefit/risk ratio for the mother and the foetus.

Some corticosteroids cross the placental barrier. A retrospective study detected a greater incidence of low birth weight in children born to mothers receiving corticosteroids. In humans, the risk of low birth weight appears to be dose dependent and can be minimised by administrating lower doses of corticosteroids. Children born to mothers who received large doses of corticosteroids during pregnancy should be carefully observed and assessed for signs of adrenal insufficiency, although neonatal adrenal insufficiency seems rare in infants who have been exposed to corticosteroids in utero.

There is no known effect of corticosteroids on labour and delivery.

Cases of cataracts have been observed in infants born to mothers taking corticosteroids in the long term during their pregnancy.

Breastfeeding

Corticosteroids pass into breast milk may inhibit growth and disturb production of endogenous glucocorticoids in breast-fed infants.

This medicine should only be used during breastfeeding after a thorough assessment of the benefit/risk ratio for the mother and infant.

In the event of high dose and chronic therapy, breastfeeding is inadvisable.

Fertility

Impairment of fertility has been highlighted during the administration of corticosteroids in animal studies (see section 5.3).

4.7. Effects on ability to drive and use machines

The effect of corticosteroids on the ability to drive or use machines has not been systematically evaluated. Undesirable effects such as dizziness, vertigo, visual disturbances and fatigue are possible after treatment with corticosteroids. If these symptoms occur, patients should not drive or use machines.

4.8. Undesirable effects

System organ class	Undesirable effects
Infections and infestations	Opportunistic infection, infection, peritonitis†
Blood and lymphatic system disorders	Leukocytosis
Immune system disorders	Hypersensitivity (anaphylactic reactions, anaphylactoid reactions)
Endocrine disorders	Cushingoid disorders, hypopituitarism, steroid withdrawal syndrome
Metabolic and nutritional disorders	Metabolic acidosis, fluid retention, hypokalaemic alkalosis, dyslipidaemia, glucose intolerance disorders, increase in insulin needs (or those of glucose-lowering agents in diabetics), lipomatosis, increased appetite (which may cause weight gain)

Psychiatric disorders	Affective disorders (including depressed mood, euphoric mood, lability, addiction to drugs, suicidal ideation), psychotic disorders (including mania, illusion, hallucination and schizophrenia), psychotic behaviour, mental disorders, personality change, confusional state, anxiety, mood swings, abnormal behaviour, insomnia and irritability
Nervous system disorders	Epidural lipomatosis, increased intracranial pressure (with papilledema [benign intracranial hypertension]), seizure, amnesia, cognitive impairment, dizziness and headache
Eye disorders	Chorioretinopathy, cataract, glaucoma, exophthalmia, blurred vision (see section 4.4)
Ear and labyrinth disorders	Vertigo
Cardiac disorders	Congestive heart failure (in patients at risk)
Vascular disorders	Thrombotic events, thrombosis, hypertension, hypotension
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism, hiccups
Gastrointestinal disorders	Gastroduodenal ulcer (possibly with perforation or haemorrhage), intestinal perforation, gastric haemorrhage, pancreatitis, ulcerous oesophagitis, oesophagitis, abdominal distension, abdominal pain, diarrhoea, dyspepsia, nausea
Skin and subcutaneous tissue disorders	Quincke's oedema, hirsutism, petechiae, bruises, skin atrophy, erythema, hyperhidrosis, stretch marks, rash, pruritus, urticaria, acne
Musculoskeletal and connective tissue disorders	Muscular weakness, myalgia, myopathy, muscle atrophy, osteoporosis, osteonecrosis, pathological fracture, neuropathic arthropathy, arthralgia, delayed growth
Reproductive system and breast disorders	Menstrual irregularities
General disorders and administration site conditions	Delayed wound healing, peripheral oedema, fatigue, malaise
Investigations	Increase in intraocular pressure, decrease in blood potassium, increase in urine calcium, decreased glucose tolerance, increased liver enzymes: alanine aminotransferase and aspartate aminotransferase, increased alkaline phosphatase in the blood, increased uric acid, suppression of reactions to skin tests*.
Injury, poisoning and procedural complications	Vertebral fracture by compression, tendon rupture

* is not a MedDRA term

† Peritonitis may be the main sign or symptom of a gastrointestinal disorder such as a perforation, an obstruction or pancreatitis (see section 4.4 Special warnings and precautions for use).

Reporting of suspected adverse reactions.

Reporting suspected side effects after authorisation of the medicinal product is important. It facilitates the continuous monitoring of the risk/benefit ratio for the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9. Overdose

Cases of acute toxicity and/or death reported following an overdose of corticosteroids are rare.

In the case of overdose, there is no specific antidote, the treatment is symptomatic.

Methylprednisolone is dialysable.

After chronic intoxication, the onset of adrenal deficiency can be prevented by a gradual dose reduction. In this case, the patient may need monitoring and suitable therapy during episodic stress.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: GLUCOCORTICOID - SYSTEMIC USE (H - NON-SEXUAL HORMONES), ATC code: H02AB04.

Physiological glucocorticoids (cortisone and hydrocortisone) are essential metabolic hormones. Synthetic corticoids including MEDROL tablet, are mainly used for their anti-inflammatory effects; they decrease immune response at high doses. Their metabolic and sodium retention effect is less than that of hydrocortisone.

Methylprednisolone is a potent anti-inflammatory. Its anti-inflammatory potency is greater than that of prednisolone and it causes less fluid retention than the latter.

Methylprednisolone is 4 times more powerful than hydrocortisone.

5.2. Pharmacokinetic properties

The pharmacokinetic parameters of methylprednisolone are linear and independent of the route of administration. Absorption

Methylprednisolone is rapidly absorbed, and its plasma concentration reaches a maximum value at the end of approximately 1.5 to 2.3 hours on all the doses as a result of oral administration in healthy adult subjects. The absolute bioavailability of methylprednisolone in healthy subjects has been generally high (82 to 89%) as a result of oral administration. Distribution

Methylprednisolone is widely distributed in tissue, it crosses the blood-brain barrier and is secreted in milk. Its apparent distribution volume is approximately 1.4 l/kg.

Methylprednisolone protein binding is approximately 77% in humans.

Biostransformation

In humans, methylprednisolone is metabolised in the liver to inactive metabolites; the main ones are 20α-hydroxymethylprednisolone and 20β-hydroxymethylprednisolone. Hepatic metabolism is mainly carried out by CYP3A4 enzymes. (See section 4.5).

Methylprednisolone, like many CYP3A4 substrates, may also be a substrate of P-glycoprotein, a transport protein of the family of ABCs (ATP-binding cassette), which can have an impact on tissue distribution and interactions with other medicines.Elimination

The total average elimination half-life of methylprednisolone is between 1.8 and 5.2 hours. Total clearance is approximately 5 to 6 ml/min/kg.

5.3. Preclinical safety data

The non-clinical; database as well as evidence concerning safety gleaned over years of clinical and pharmacovigilance experience demonstrate the safety of methylprednisolone tablets as a potent anti-inflammatory agent in the event of short-term inflammatory disorders.

Based on conventional pharmacology safety studies, repeated dose toxicity in mice, rats, rabbits and dogs receiving the substance intravenously, intraperitoneally, subcutaneously and intramuscularly did not demonstrate any expected risk. The toxicities observed in repeated dose studies are as expected with continuous exposure to exogenous steroids.

Carcinogenic potential

The carcinogenicity of methylprednisolone has not been properly assessed in studies in rodents. Mixed results have been obtained with other glucocorticoids tested for their carcinogenic potential in mice and rats. However, the published data indicate that several related glucocorticoids, including budesonide, prednisolone and, triamcinolone acetonide may increase the incidence of adenomas and hepatocellular carcinomas after oral administration in the drinking water of male rats. These tumorigenic effects have been observed at doses that were lower than the usual clinical doses on a mg/m^2 basis.

Mutagenic potential

The genotoxicity of methylprednisolone has not been officially assessed. However, methylprednisolone sulfonate, which has a structure similar to methylprednisolone, was not mutagenic with or without metabolic activation in *Salmonella typhimurium* at doses of 250 to 2 000 µg/plate, or via the test for gene mutation in mammalian cells using Chinese hamster ovary cells at doses of 2000 to 10000 µg/ml. Methylprednisolone suleptanate did not cause unscheduled DNA synthesis in the primary hepatocytes of rats at doses of 5 to 1000 µg/ml. In addition, a review of the published data indicates that prednisolone farnesylate, which has a similar structure to methylprednisolone, was not mutagenic with or without metabolic activation in strains of *Salmonella typhimurium* and *Escherichia coli* at doses of 312 to 5000 µg/plate. In a lineage of Chinese hamster fibroblastic cells, prednisolone farnesylate led to a slight increase in the incidence of structural chromosomal aberrations with metabolic activation at the highest concentration tested 1500 µg/ml.

Reproductive toxicity

A reduction in fertility was highlighted during the administration of corticosteroids in rats. Doses of corticosterone of 0, 10 and 25 mg/kg/day were administered to male rats by subcutaneous injection once a day for 6 weeks and these male rats were mated with untreated females. The high dose was reduced to 20 mg/kg/day after the 15th day. A decrease in the copulatory plug was observed, which may have been secondary to a decrease in the weight of the accessory organs. The number of implantations and viable foetuses was reduced.

Corticosteroids have been shown to be teratogenic in a number of species after administration of doses equivalent to that in humans. In the animal studies on reproduction, glucocorticoids such as methylprednisolone increased the incidence of malformations (cleft palate, skeletal malformations), embryo-foetal lethality (for example, increase in resorptions), and intrauterine growth retardation.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

MEDROL 4mg

Lactose monohydrate, sucrose, calcium stearate, anhydrous maize starch, maize starch.

MEDROL 16mg

Lactose, sucrose, liquid paraffin, calcium stearate, maize starch.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

No special precautions for storage.

6.5. Nature and contents of container

MEDROL 4mg

30 tablets in packs (PVC/Aluminium).

MEDROL 16mg

20 tablets in packs (PVC/Aluminium).

6.6. Special precautions for disposal and other handling

No special requirements.

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

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURER

Marketing authorisation holder: PFIZER HOLDING FRANCE
23-25, AVENUE DU DOCTEUR LANNELONGUE
75014 PARISFRANCE

Manufacturer:
PFIZER ITALIA S.R.L.
LocalitA Marino del Tronto
63100 Ascoli Piceno (AP)
ITALY

Or

VALDEPHARM
PARC INDUSTRIEL D'INCARVILLE
27100 VAL-DE-REUIL
FRANCE

CONTENTS OF CONTAINER:
MEDROL 4mg, tablets. Box of 30 tablets
MEDROL 16MG, TABLETS. BOX OF 20 tablets

LOCAL REPRESENTATIVE:
PFIZER AFRIQUE DE L'OUEST

ADMINISTRATIVE ADDRESS:
PFIZER AFRIQUE DE L'OUEST
Regus Plateau 3rd Floor
Azur 15 Building
12 Boulevard Djily Mbaye
Dakar Sénégal BP 3857 Dakar RP

8. DATE OF REVISION OF THE TEXT

19 November 2020

GENERAL CLASSIFICATION FOR SUPPLY

List I