SOLUMEDROL 120 mg/2 mL, freeze-dried powder and solution for parenteral use
Methylprednisolone hemisuccinate

Date: March 2022. Version no. 10

Reference Market: France

West Africa

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

SOLUMEDROL 120 mg/2 mL, freeze-dried powder and solution for parenteral use

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Freeze-dried powder

Methylprednisolone hemisuccinate ..... 152.06 mg

Quantity corresponding to methylprednisolone base ..... 120.00 mg

Per vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Freeze-dried powder and solution for parenteral use.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

The indications are:

- for corticotherapy when oral administration is not possible (vomiting, gastric aspiration, impaired consciousness) and the parenteral route is necessary;
- disorders requiring a rapid therapeutic effect:
  - **Allergies:**
    - severe angio-oedema along with antihistamines,
    - anaphylactic shock with adrenaline.
  - **Infections:**
    - severe typhoid fever, particularly with mental confusion, shock, coma,
    - laryngismus stridulus (subglottic laryngitis) in children.
  - **Neurological:**
    - cerebral oedema (tumours, toxoplasmic abscesses, etc.)
  - **ENT:**
    - laryngitis dyspnoea.

4.2. Posology and method of administration

This medicinal product is not intended for inhalation using a nebuliser.

Anti-inflammatory equivalence (equipotency) for 5 mg prednisone: 4 mg methylprednisolone.

Posology

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

After mixing, the obtained solution can be administered via IV:

- either directly via slow injection, minimum duration: 20 to 30 minutes (see section 4.8),
- or by IV perfusion after dilution in an isotonic solution of sodium chloride or glucose.

When IV perfusion cannot be used, administration can be made by deep IM injection under strict aseptic conditions.

The dosage is 120 mg per day. In very exceptional cases, this dose may be repeated.

Method of administration

INTRAVENOUS OR INTRAMUSCULAR INJECTIONS

FOR ADULTS ONLY

4.3. Contraindications

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

- any infectious condition, excluding the specific indications (see section 4.1),
- certain progressive viruses (notably hepatitis, herpes, chicken pox, herpes zoster),
- psychotic conditions not yet controlled with treatment,
- live vaccines or attenuated live vaccines (for yellow fever, tuberculosis, rotavirus, measles, mumps, rubella, chickenpox, herpes zoster, flu) in patients receiving doses greater than 10 mg/day prednisone equivalent (or > 2 mg/kg/day in children or > 20 mg/day in children weighing more than 10 kg) for more than two weeks, and for corticosteroid “boluses” (except by inhalation and topical routes), and for three months after discontinuation of the corticosteroid therapy: risk of potentially fatal generalised vaccine disease,
- hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- in intrathecal administration,
- in epidural administration,
- haemostasis disorders or ongoing anticoagulant treatment in case of intramuscular injection.

This medicinal product is generally contraindicated in combination with acetylsalicylic acid in anti-inflammatory doses with mifamurtide or with potent CYP3A4 inhibitors (see section 4.5).

4.4. Special warnings and precautions for use

Special warnings

Immunosuppressive effects/increased susceptibility to infection

Corticotherapy may promote the occurrence of various infectious complications notably due to bacteria, yeasts and parasites. There is a significant risk of the occurrence of malignant strongyloidiasis. 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.

Subjects treated with immunosuppressants are more sensitive to infections than healthy subjects. Patients must avoid contact with people who have chickenpox or measles. These viruses may become progressively more severe, even fatal, in children who are not immunised or in adults using corticosteroids.

The administration of live vaccines or attenuated live vaccines is contraindicated in patients receiving doses greater than 10 mg/day prednisone equivalent (or > 2 mg/kg/day in children or > 20 mg/day in children weighing more than 10 kg) for more than two weeks and for corticosteroid “boluses” (except by inhalation and topical routes), and for three months after discontinuation of corticosteroid therapy (see sections 4.3 and 4.5). Non-live or inactivated vaccines may be administered in patients receiving immunosuppressive doses of corticosteroids. However, the response to such vaccines may be diminished. The immunisation procedures indicated may be carried out in patients receiving non-immunosuppressive doses of corticosteroids.

Before commencing treatment, it is important to rule out any possibility of a visceral focus, notably tuberculosis, and to monitor 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.

The use of corticosteroids in active tuberculosis should be limited to cases of fulminant or disseminated tuberculosis in which corticosteroids are used to control the disease in combination with an appropriate anti-tuberculosis treatment.

Cases of Kaposi's sarcoma have been reported in patients treated with corticosteroids. Discontinuation of corticosteroids may result in clinical remission.

The role of corticosteroids in septic shock has been controversial, with early studies reporting both beneficial and harmful effects. More recently, it has been shown that supplemental treatment with corticosteroids may be beneficial in patients with established septic shock who exhibit adrenal insufficiency. However, their routine use in septic shock is not recommended and a systematic review has concluded that use of corticosteroids in high doses for a short period of time was not recommended. However, meta-analyses and another review suggests that longer low-dose courses (5-11 days) of corticosteroids might reduce mortality, particularly in patients with septic shock who are sensitive to vasoconstrictors.

Effects on the immune system

Allergic reactions may occur. Rare cases of skin reactions and anaphylactic/anaphylactoid reactions have occurred in patients treated with corticotherapy. Special attention must be given prior to administration, particularly in subjects with atopic history.

Endocrine effects

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

Pharmacological doses of corticosteroids administered for prolonged periods may result in inhibition of the hypothalamic-pituitary-adrenal axis (secondary adrenocortical insufficiency). The significance and duration of adrenocortical insufficiency varies from patient to patient and depends on the dose, frequency, time of administration and treatment duration with glucocorticoids. This effect may be minimised by administering the treatment every other day.

In addition, the abrupt discontinuation of corticosteroids may cause potentially fatal acute adrenal insufficiency.

Secondary medicinal product-induced adrenocortical insufficiency may therefore be minimised by gradual reduction of the dosage. This type of relative insufficiency may persist for months after discontinuation of therapy. Hormone therapy should therefore be restarted in any situation of stress occurring during that period.

A steroid “withdrawal syndrome”, seemingly 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, desquamation, myalgia, weight loss, and/or hypotension. It appears that these effects are due to the sudden change in glucocorticoid concentration rather than to low corticosteroid levels.

As glucocorticoids may result in or aggravate Cushing's syndrome, their use should be avoided in patients with Cushing’s disease.

Corticosteroids have an increased effect in patients with hypothyroidism.

Metabolism and nutrition

Corticosteroids, including methylprednisolone, may increase blood glucose, worsen pre-existing diabetes or predispose patients receiving long-term corticosteroid therapy to diabetes.

When corticotherapy is necessary, diabetes is not a contraindication, but the treatment can cause an imbalance. Reassessment of care is recommended.

Psychiatric effects

Psychiatric disorders may occur when using corticosteroids, such as euphoria, insomnia, mood swings, personality changes, severe depression and also clear psychotic events. In addition, existing emotional instability or psychotic tendencies may worsen with corticotherapy.

Potentially severe psychiatric adverse reactions may occur with systemic steroids. These symptoms typically emerge within a few days or weeks of starting treatment. Although a specific treatment may be necessary in some cases, most of these reactions regress after reducing the dose or discontinuing treatment. Psychological effects have been reported when discontinuing corticosteroids; their frequency is unknown. Patients/caregivers should be encouraged to seek medical attention if psychological symptoms occur in the patient, especially if depression or suicidal ideation is suspected. Patients/caregivers should be alert to possible psychiatric disturbances that may occur either during or immediately after dose reduction or withdrawal of systemic steroids.

Nervous system effects

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

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

Although controlled clinical trials have demonstrated the efficacy of corticosteroids in accelerating the resolution of acute clinical episodes in multiple sclerosis, they do not show that corticosteroids influence the final outcome or natural evolution of the disease. Studies indicate that relatively high doses of corticosteroids are necessary to obtain a significant effect.

Severe medical events have been reported in association with intrathecal/epidural routes of administration (see section 4.8).

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

Ocular effects

Corticosteroids should be used with caution in patients with ocular herpes due to possible corneal perforation.

Prolonged use of corticosteroids may cause posterior subcapsular cataracts and nuclear cataracts (notably in children), an exophthalmia or increased intraocular pressure, may result in glaucoma with a possible impairment of the optical nerves. The occurrence of secondary fungal or viral ocular infections may also be increased in patients using glucocorticoids.

Corticosteroid treatment has been associated with serious central chorioretinopathy, which may cause retinal detachment.

Visual disturbances

Visual disturbances can occur during systemic or local corticosteroid treatment. In cases of blurred vision or the onset of any other visual symptom occurring during corticosteroid treatment, an eye examination is required, in particular to investigate cataracts, glaucoma, or more rare damage, such as central serous chorioretinopathy, described with the administration of systemic or local corticosteroid treatment.

Cardiac effects

The undesirable 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 treatment and use at high doses. Therefore, corticosteroids should be employed judiciously in such patients and special attention should be given to risk modification and additional cardiac

monitoring if necessary. A low-dose treatment or every other day can reduce the incidence of corticotherapy complications.

Cases of cardiac arrhythmia and/or circulatory collapse and/or cardiac arrest following a rapid intravenous administration of methylprednisolone hemisuccinate at high doses has been reported (more than 0.5 g administered over a period of less than 10 minutes). Bradycardia has been reported either during or after the administration of methylprednisolone hemisuccinate at high doses, but may not be related to the speed or duration of infusion.

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

Vascular effects

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

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

When corticotherapy is necessary, hypertension is not a contraindication, but the treatment can cause an imbalance. Reassessment of care is recommended.

Gastrointestinal effects

High doses of corticosteroids may cause acute pancreatitis.

There is no consensus on the fact that corticosteroids in themselves are responsible for gastro-duodenal ulcers encountered during treatment. However, glucocorticoids can mask the symptoms of gastro-duodenal ulcer so that perforation or haemorrhage may occur without significant pain.

Corticotherapy may mask peritonitis or other signs and symptoms associated with gastrointestinal disorders such as perforation, obstruction or pancreatitis.

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

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.

The use of corticosteroids requires specially adapted monitoring, in patients with ulcerative colitis and particularly in cases of risk of perforation, abscess or other pyogenic infections, diverticulitis, recent intestinal anastomosis, evolving or latent gastro-duodenal ulcer.

Hepatobiliary effects

Cyclic IV injections of methylprednisolone in high doses (usually 1 g/day), over a short interval and during several days may induce hepatic impairment, such as acute hepatitis. The occurrence of acute hepatitis may be delayed by several weeks or more. The resolution of the undesirable event has been observed after discontinuing treatment.

Medicinal product-induced hepatic lesions including acute hepatitis or an increase in hepatic enzymes may be a result of the intravenous administration of methylprednisolone in cyclic intermittent treatment (usually at an initial dose of ≥ 1 g/day). Rare cases of hepatotoxicity have been reported. Its appearance may be delayed by several weeks or more. In the majority of case studies, these adverse reactions resolved after discontinuation of the treatment. Adequate monitoring is therefore required.

Musculoskeletal effects

Acute myopathy has been reported with 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. Increased creatine kinase may be observed. Clinical improvement or recovery after discontinuing corticosteroids may require several weeks to several years.

Osteoporosis is a common undesirable effect, but rarely recognised as an undesirable effect associated with long-term use of glucocorticoids in high doses.

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

Oral or injectable corticosteroids may promote the onset of tendinopathy, even tendon rupture (rare). This risk increases if co-prescribed with fluoroquinolones and in dialysis patients with secondary hyperparathyroidism or who have undergone a kidney transplant.

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 insufficiency.

Investigations

Average to high doses of hydrocortisone or cortisone may cause an increase in blood pressure, sodium and water retention and increased excretion of potassium. These effects are less likely to occur with synthetic derivatives, except when used in high doses. A low sodium diet and potassium supplements may be required.

All corticosteroids increase calcium excretion.

Injury, poisoning and procedural complications

Corticosteroids for oral use are contraindicated in the treatment of cranial traumas, and should therefore not be used in such cases.

A multicentre study has shown an increase of early (by two weeks) and late (by six months) mortality after a cranial trauma in patients receiving methylprednisolone hemisuccinate, compared to the placebo group. A causal relationship with methylprednisolone hemisuccinate treatment has not been established.

Use in children

The growth and development of infants and children receiving prolonged corticotherapy should be carefully observed.

Growth may be stunted in children receiving a fractioned daily dose of glucocorticoids in the long term. This protocol for use must be limited to the most urgent indications. Using glucocorticoids every other day generally prevents or minimizes this side effect.

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

High doses of corticosteroids may result in pancreatitis in children.

Hypertrophic cardiomyopathies have been reported after systemic administration of glucocorticoids including methylprednisolone to prematurely born infants; therefore, appropriate diagnostic evaluation and monitoring of cardiac function and structure, in infants treated with methylprednisolone for systemic use, is warranted.

Others

Complications of treatment with glucocorticoids are dependent on the dose and duration of treatment. Therefore, a benefit/risk assessment should be made on a case-by-case basis,

both on the dose and duration of treatment as well as the use of the daily or intermittent therapy.

The lowest possible dose of corticosteroids should be used to control the condition of the treated patient and when the dose reduction is possible, which should be done progressively.

Acetylsalicylic acid (aspirin) and non-steroidal anti-inflammatory drugs should be used with caution in combination with corticosteroids.

Concomitant administration with CYP3A inhibitors, including products containing cobicistat, is not expected to increase the risk of systemic side effects. This combination should be avoided unless the benefits outweigh the increased risk of systemic side effects related to corticosteroids, in which case the patients should be monitored for systemic side effects related to corticosteroids (see section 4.5).

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

Athletes should be aware that this medicinal product contains methylprednisolone; this active ingredient is included on the list of doping substances.

Excipient information

This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

Precautions for use

Oral treatment must follow as soon as possible.

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.

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

HYPOKALAEMICS

Hypokalaemia can lead to heart rhythm disorders (particularly torsades de pointes) and can increase the toxicity of certain medicines, for example digoxin. Therefore, medicines that can lead to hypokalaemia 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 (CYP) enzymes and is primarily metabolised by the CYP3A4 enzyme. CYP3A4 is the dominant enzyme of the most abundant CYP subfamily in the liver of adult subjects. 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 (as well as other medicinal products) alter glucocorticoid metabolism by induction or inhibition of this enzyme.

CYP3A4 inhibitors: [Antibiotics (isoniazide), anti-emetics (aprepitant, fosaprepitant), antifungals (itraconazole, ketoconazole), antivirals (HIV protease inhibitors: indinavir, ritonavir agents of pharmacokinetic potentiation (cobicistat), calcium antagonists (diltiazem), oral contraceptives (ethinyl oestradiol, norethindrone), grapefruit juice, immunosuppressants (ciclosporin), macrolide antibiotics (clarythromycin, erythromycin, troleandomycin)]:

Medicinal products that inhibit CYP3A4 enzyme activity generally decrease hepatic clearance and increase the plasma concentration of substrate medicinal products of this enzyme, such as methylprednisolone. In case of concomitant treatment with a CYP3A4 inhibitor, it is necessary to adjust the dose of methylprednisolone in order to avoid corticosteroid toxicity events.

CYP3A4 inducers: [Antibiotics, antituberculosis treatment (rifampicin), anticonvulsants (carbamazepine, phenobarbital, and phenytoin)]:

Medicinal products that induce CYP3A4 enzyme activity generally increase hepatic clearance and decrease the plasma concentration of substrate medicinal products of this enzyme. In cases of concomitant administration, an increase in the methylprednisolone dose may be necessary to obtain the desired results.

CYP3A4 substrates: [Anticonvulsants (carbamazepine), anti-emetics (aprepitant, fosaprepitant), antifungals (itraconazole, ketoconazole), antivirals (HIV protease inhibitors: indinavir, ritonavir), calcium antagonists (diltiazem), oral contraceptives (ethinyl oestradiol, norethindrone), immunosuppressants (ciclosporin, cyclophosphamide, tacrolimus), macrolide antibiotics (clarythromycin, erythromycin)]:

In the presence of another CYP3A4 substrate, the hepatic clearance of methylprednisolone may be affected. The dosage should therefore be adjusted accordingly. A co-administration may increase the probability of undesirable effects associated with either of these medicinal products administered alone.

Contraindicated combinations

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

In patients receiving doses greater than 10 mg/day prednisone equivalent (or > 2 mg/kg/day in children or > 20 mg/day in children weighing more than 10 kg) for more than two weeks, and for corticosteroid “boluses” (except by inhalation and topical routes), and for three months after discontinuation of corticosteroid therapy: risk of potentially fatal generalised vaccine disease.

Inadvisable combinations

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

Increased risk of bleeding.

Furthermore, 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, which 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 may cause torsades de pointes

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

Correct all hypokalaemia before administering the product and carry out clinical, electrolytic and ECG monitoring.

+ Oral anticoagulants such as acenocoumarol, apixaban, dabigatran, fluindione, phenindione, rivaroxaban, warfarin

Glucocorticoids (systemic and rectal routes): possible impact of corticosteroid therapy on the metabolism of the vitamin K antagonist and on that of coagulation factors.

There are reports of enhanced as well as diminished effects of anticoagulants when given concurrently with corticosteroids.

Risk of bleeding specific to corticosteroid therapy (digestive mucosa, vascular fragility) at high doses or for prolonged periods of more than 10 days.

When the combination is justified, increase surveillance: where appropriate, laboratory controls at 8 days with vitamin K antagonists, then every 15 days during corticosteroid therapy and following its discontinuation.

+ Vitamin K antagonists (acenocoumarol, fluindione, warfarin)

For doses of 0.5 to 1 g of methylprednisolone administered as a bolus: increase in the vitamin K antagonist effect and the risk of haemorrhage.

Check INR 2 to 4 days after the bolus of methylprednisolone or in the presence of any haemorrhagic signs.

+ Other hypokalaemic drugs (hypokalaemic diuretics alone or in combination, stimulant laxatives, IV amphotericin B)

Increased risk of hypokalaemia

Monitoring of serum potassium levels and correction if necessary.

+ Digitalis (digoxin)

Hypokalaemia favouring the toxic effects of digitalis.

Correct any hypokalaemia beforehand and carry out clinical, electrolyte and ECG monitoring.

+ 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)

Reduction in the plasma levels and efficacy of corticosteroids through an increase in their hepatic metabolism by the inducer; the consequences are particularly marked in patients with Addison's disease treated with hydrocortisone or in the event of transplantation.

Clinical and biological surveillance, adjustment of the corticosteroid dosage during treatment with the inducer and following its discontinuation.

+ Antidiabetics

Elevation of blood sugar levels, with ketosis in some cases (reduction in carbohydrate tolerance by corticosteroids).

Warn the patient and increase self-monitoring of blood and urine values, particularly at the beginning of treatment. Adjust the dosage of the antidiabetic agent if necessary, during treatment with corticosteroids and following its discontinuation.

+ Isoniazid (described for prednisolone)

Reduction in plasma isoniazid levels. Suggested mechanism: increase in the hepatic metabolism of isoniazid, potentially by acetylation, and reduction in that of glucocorticoids and potential effect on isoniazid clearance.

Clinical and biological surveillance.

+ Cobimetinib

Increased risk of bleeding.

Clinical monitoring.

Combinations to be taken into account

+ Acetylsalicylic acid in antalgic or antipyretic doses ≥ 500 mg per dose and/or < 3 g per day

Increased risk of haemorrhage.

+ Non-steroid anti-inflammatories

Increased risk of ulceration and gastrointestinal haemorrhage.

+ Antihypertensive agents

Reduction in the antihypertensive effect (water and salt retention caused by corticosteroids).

+ Ciclosporin

With intravenously administered methylprednisolone: possible increase in blood levels of ciclosporin and creatinine.

The relevant mechanism: reduction of the hepatic elimination of ciclosporin.

Therefore, it is possible that adverse events associated with the use of either drug alone may be more likely to occur upon co-administration

Convulsions have been reported with concurrent use of methylprednisolone and ciclosporin.

+ Fluoroquinolones

Possible increase in the risk of tendon disease, or even tendon rupture (exceptional), particularly in patients receiving long-term corticosteroid therapy.

+ Alpha interferon

Risk of inhibition of the action of interferon.

+ Non-depolarising neuromuscular blocking agents:

With intravenously administered glucocorticoids: risk of severe myopathy, reversible after a potentially long period (several months) (see section 4.4).

Antagonism of the neuromuscular blocking effects of pancuronium and vecuronium has been reported in patients taking corticosteroids. This interaction may be expected with all competitive neuromuscular blockers.

+ Aromatase inhibitors (aminoglutethimide)

Aminoglutethimide-induced adrenal suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment.

+ Anticholinesterases

Steroids may reduce the effects of anticholinesterases in myasthenia gravis.

+ Antivirals (**HIV protease inhibitors)**

Corticosteroids may induce the metabolism of HIV protease inhibitors resulting in reduced plasma concentrations.

+ Heparin

Increased risk of bleeding.

Incompatibilities

To avoid compatibility and stability problems, it is recommended that methylprednisolone sodium succinate be administered separately from other compounds that are administered via the IV route of administration. Drugs that are physically incompatible in solution with methylprednisolone sodium succinate include, but are not limited to: allopurinol sodium, doxapram hydrochloride, tigecycline, diltiazem hydrochloride, calcium gluconate, vecuronium bromide, rocuronium bromide, cisatracurium besylate, glycopyrrolate, propofol.

4.6. Fertility, pregnancy and lactation

Pregnancy

In animals experiments, a teratogenic effect has been observed for corticosteroids when they are administered in females at high doses. However, corticosteroids do not appear to cause congenital abnormalities when they are administered in pregnant women. Given that no adequate human reproduction study has been carried out with methylprednisolone hemisuccinate, this medicinal product will only be used during pregnancy after a thorough benefit/risk assessment for the mother and the fœtus.

In humans, certain corticosteroids easily cross the placenta. However, epidemiological studies have not detected any risk of malformation linked to taking corticosteroids during the first trimester.

A retrospective study found an increased incidence of low birth weight in infants born to mothers receiving corticosteroids. In men, the risk of low birth weight appears to be dose-dependent et can be minimised by the administration of lower corticosteroid doses. Although neonatal adrenal insufficiency seems to be rare in infants having been exposed in utero to corticosteroids, neonates of mothers who received substantial doses of corticosteroids during pregnancy should be carefully observed and evaluated for signs of adrenal insufficiency.

There is no known effect of corticosteroids on labour or childbirth.

After long-term corticotherapy during pregnancy, cases of cataracts have been observed in infants.

Breast-feeding

Corticosteroids pass into breast milk and may inhibit growth and disturb endogenous production of glucocorticoids in breast-fed infants. This medicinal product should only be used during breast-feeding after a thorough benefit/risk assessment for the mother and the infant.

In case of chronic treatment at high doses, breast-feeding is inadvisable.

Fertility

Changes in fertility have been demonstrated during the administration of corticosteroids in studies conducted in animals (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 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 vehicles or operate machinery.

4.8. Undesirable effects

The following adverse reactions have been reported during administration contraindicated by intrathecal/epidural route: arachnoiditis, functional gastrointestinal disorder/bladder

dysfunction, headache, meningitis, paraparesis/paraplegia, convulsions, sensory disturbances.

System organ class	Undesirable effects
Infections and infestations	Opportunist 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
Metabolism and nutrition disorders	Metabolic acidosis, fluid retention, hypokalaemic alkalosis, dyslipidaemia, glucose intolerance disorders, increase in insulin needs (or those of glucose-lowering agents in diabetics), increase in appetite (which may cause weight gain)
Psychiatric disorders	Emotional disorders (including depressive mood, euphoric mood, emotional lability, drug dependence, suicidal thoughts), psychotic disorders (including mania, delirium, hallucinations, schizophrenia), mental disorders, changes in personality, confusion, anxiety, mood swings, abnormal behaviour, insomnia, irritability
Nervous system disorders	Epidural lipomatosis, increase of intracranial pressure (with papilloedema [benign intracranial hypertension]), seizures, amnesia, cognitive disorders, dizziness, headaches
Eye disorders	Chorioretinopathy, cataracts, glaucoma, exophthalmia, blurred vision (see section 4.4)
Ear and labyrinth disorders	Vertigo
Cardiac disorders	Congestive heart failure (in susceptible patients), arrhythmia, hypertrophic cardiomyopathy in premature infants (see section 4.4)
Vascular disorders	Thrombosis, hypertension, hypotension, thrombotic events
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism, hiccups
Gastrointestinal disorders	Gastro-duodenal ulcer (possibly with perforation or haemorrhage), intestinal perforation, gastric haemorrhage, pancreatitis, ulcerous oesophagitis, oesophagitis, abdominal distension, abdominal pain, diarrhoea, dyspepsia, nausea
Hepatobiliary disorders	Hepatitis**
Skin and subcutaneous tissue disorders	Quincke's oedema, hirsutism, petechiae, ecchymosis, dermatrophy, erythema, hyperhidrosis, striae, rash, pruritus, urticaria, acne, cutaneous hypopigmentation
Musculoskeletal and connective tissue disorders	Muscle weakness, myalgia, myopathy, muscle atrophy, osteoporosis, osteonecrosis, pathological fractures, neuropathic arthropathy, arthralgia, growth disorder

Reproductive system and breast disorders	Menstrual irregularities
General disorders and administration site conditions	Delayed healing, peripheral oedema, fatigue, malaise, reaction at the injection site
Investigations	Increased intraocular pressure, decreased glucose tolerance, decreased blood potassium level, increased urinary calcium, increased alanine aminotransferase, increased aspartate aminotransferase, increased alkaline phosphatase in the blood, increased uricaemia, suppression of reactions to skin tests*
Injury, poisoning and procedural complications	Vertebral fracture by compression, tendon rupture

* not a MedDRA term
**Cases of hepatitis reported with IV administration (see section 4.4).
Peritonitis may be the primary presenting sign or symptom of a gastrointestinal disorder such as perforation, obstruction or pancreatitis (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 should report any suspected undesirable effects via the national reporting system.

4.9. Overdose

There is no acute clinical overdose syndrome related to corticosteroids. Reported cases of acute toxicity and/or death following overdose with corticosteroids are rare. In case of overdose, no specific antidote is available; treatment is symptomatic. Methylprednisolone is dialysable.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: CORTICOSTEROIDS IN NON-COMBINED, SYSTEMIC USE, ATC Code: H02AB04.

Physiological glucocorticoids (cortisone and hydrocortisone) are essential metabolic hormones. Synthetic corticosteroids, including methylprednisolone, are mainly used for their anti-inflammatory effect. At high doses, they reduce the immune response. Their metabolic and sodium retention effect is lower than that of hydrocortisone.

Methylprednisolone is a powerful anti-inflammatory. Its anti-inflammatory potency is greater than prednisolone and causes less salt and water retention than prednisolone.

Methylprednisolone is four times more potent than hydrocortisone.

5.2. Pharmacokinetic properties

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

Absorption

After administration of a 40 mg dose of methylprednisolone sodium succinate by intramuscular (IM) route in 14 healthy adult male volunteers, the average concentration peak of 454 ng/mL was reached within 1 hour. At 12 hours, the plasma concentration of

methylprednisolone decreased to 31.9 ng/mL. Methylprednisolone has not been detected 18 hours after administration. Based on the area under the concentration-time curve, an indication of the total quantity of medicinal product absorbed, the intramuscular methylprednisolone sodium succinate was considered equivalent to the same dose of methylprednisolone administered intravenously (IV).

The results of one study showed that methylprednisolone sodium succinate ester is rapidly and widely transformed into activated methylprednisolone after any route of administration. The absorption level of free methylprednisolone after IV and IM administration was considered equivalent insignificantly superior compared to after administration with oral solution and methylprednisolone tablets taken orally. Given that the absorption level of methylprednisolone after IV and IM administration was equivalent despite the larger quantity of hemisuccinate ester attained systemically after IV administration, it seems that ester is converted into tissue after IM injection with a subsequent absorption in free methylprednisolone.

Distribution

Diffusion is fast. Methylprednisolone is widely distributed in the tissues, crossing the blood-brain barrier and is secreted in the milk. Its distribution volume seems to be approximately 1.4 L/kg. The binding rate of methylprednisolone to plasma proteins is approximately 77% in humans.

Biotransformation

In humans, methylprednisolone is metabolised in the liver by inactive metabolites; the principal metabolites are 20α-hydroxymethylprednisolone and 20β-hydroxymethylprednisolone. Hepatic metabolism is primarily carried out through CYP3A4 enzymes. (see section 4.5).

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

Elimination

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

Excretion is both urinary and biliary.

5.3. Preclinical safety data

Conventional pharmacology safety and repeated-dose toxicity studies revealed no unexpected risk. The toxicity levels observed in repeated-dose studies are as expected with a continuous exposure to exogenous steroids.

CarcinogenicityCarcinogenesis

The carcinogenicity of methylprednisolone has not been properly evaluated through studies in rodents. Variable results have been obtained with other glucocorticoids tested for their carcinogenic potential in mice and rats. However, published data indicates 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 in doses that were lower than the usual clinical doses on a mg/m^2 basis.

Mutagenicity

The genotoxicity of methylprednisolone has not been properly evaluated. However, methylprednisolone sulphonate, which has a similar structure to methylprednisolone, was not mutagenic with or without metabolic activation in *Salmonella typhimurium* at doses between

250 and 2,000 µg/plate, or via the gene mutation test on mammalian cells with Chinese hamster ovary cells at doses between 2,000 and 10,000 µg/mL. Methylprednisolone sulphonate did not induce unscheduled DNA synthesis in the primary hepatocytes of rats at doses between 5 and 1,000 µg/mL. In addition, a review of published data indicates that farnesylated prednisolone, which has a similar structure to methylprednisolone, was not mutagenic with or without metabolic activation in *Salmonella typhimurium* and *Escherichia coli* strains at doses between 312 and 5,000 µg/plate. In a Chinese hamster fibroblast cell line, farnesylated prednisolone resulted in a slight increase of incidence for structural chromosomal aberrations with metabolic activation at the highest tested concentration of 1,500 µg/mL.

Reproductive toxicity

A reduction in fertility has been demonstrated during the administration of corticosteroids in rats. Corticosterone doses of 0, 10 and 25 mg/kg/day were administered in male rats by subcutaneous injection once daily for 6 weeks, and these male rats were paired with untreated females. The high dose was reduced to 20 mg/kg/day after the 15th day. A decrease in size of the copulatory plug was observed, which may have been secondary to a decrease in 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 equivalent doses in humans. In animal studies on reproduction, glucocorticoids, such as methylprednisolone, were found to increase the incidence of malformations (cleft palate, skeletal malformations), embryo foetal lethality (e.g. increased resorptions), and delayed intrauterine growth.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

SOLUMEDROL 120 mg/2 mL, freeze-dried powder and solution for parenteral use

Freeze-dried powder

Anhydrous monosodium phosphate, anhydrous disodium phosphate, 10% sodium hydroxide solution.

Solvent

Water for injection.

6.2. Incompatibilities

Due to the absence of compatibility studies, this medicine must not be mixed with other medicines.

6.3. Shelf-life

3 years.

After opening/reconstitution/dilution: the product must be used immediately.

6.4. Special precautions for storage

- Store at a temperature below 25 °C.
- After reconstitution, the reconstituted solution should be used immediately.

6.5. Nature and contents of container

Freeze-dried powder in a vial (glass) + 2 mL of solvent in an ampoule (glass)

6.6. Special precautions for disposal and other handling

Freeze-dried powder must be reconstituted with 2 mL of water for injections.

Reconstitute using a syringe with an exterior diameter of 0.8 mm (equivalent to 21 gauge).

Use of a needle with a greater diameter may cause the cap or fragments of the cap to fall into the bottle.

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

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURER

PFIZER HOLDING FRANCE
23-25, AVENUE DU DOCTEUR LANNELONGUE
75014 PARIS
FRANCE

Manufacturer:

VALDEPHARM
PARC INDUSTRIEL D'INCARVILLE
PARC DE LA FRINGALE - CS 10606
27106 VAL-DE-REUIL CEDEX
FRANCE

Presentations:

Solumedrol 120 mg/2 mL, freeze-dried powder and solution for parenteral use. Package of 1 bottle (glass) and one ampoule (glass)

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. GENERAL CLASSIFICATION FOR SUPPLY

List I.

9. DATE OF REVISION TEXT

04 October 2021.