SUMMARY OF PRODUCT CHARACTERISTICS

Medicinal product subject to medical prescription. The first administration must be done in a hospital.

1. NAME OF THE MEDICINAL PRODUCT

METHYLPREDNISOLONE MYLAN 1 g, lyophilized powder for solution for injection (I.V.)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Methylprednisolone hemisuccinate: ……1267.00 mg
Quantity equivalent to methylprednisolone base: ……1000.00 mg
Per vial

Excipient with known effect: sodium
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

When corticosteroid therapy is required, but the general oral administration route connot be used (vomiting, gastric aspiration, sensorial disturbances) and the parenteral route is necessary.

4.2 Posology and method of administration

The first administration must be done in a hospital.

5 mg of prednisone is equivalent in terms of anti-inflammatory potency to 4 mg of methylprednisolone.

This proprietary medicinal product is not suitable for inhalation using a nebulizer.

This drug is reserved for cases requiring high dose corticosteroid therapy.

Dosage~~:~~
- acute symptoms of rheumatoid arthritis, extra-renal symptoms of certain systemic diseases, certain cases of systemic necrotizing vasculitis, initial treatment for certain cases of glomerulopathy: 500 mg to 1 g per day,
- organ transplantation, graft rejection: 10 to 15 mg/kg/day,
- graft versus host reaction: 10 to 20 mg/kg/day and up to 500 mg/m² every 6 hours for 48 hours.

The powder is mixed with 15.6 ml of water for injections and the resulting solution should be administered intravenously:
- either directly by slow injection, minimum duration = 20 to 30 minutes (see section 4.8).
- or by infusion after dilution in isotonic sodium chloride or glucose solution for injection.

Such high dose corticosteroid therapy is generally limited to 3 to 5 days.

4.3 Contraindications

This drug is generally contraindicated in the following situations: (however, there is no absolute contraindication if corticosteroid therapy is vitally indicated).
- any infection,
- certain active viruses (especially hepatitis, herpes, chickenpox, herpes zoster),
- psychotic states not yet controlled by treatment,
- live vaccines,
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

It is generally inadvisable to use this drug in combination with non antiarrhythmic drugs that produce atypical ventricular tachycardia (see section 4.5).

4.4 Special warnings and precautions for use

Warnings
Since rare cases of pseudo-anaphylactic reactions have occurred in patients treated with parenteral corticosteroid therapy, special attention must be paid before any administration to subjects presenting with an allergic diathesis.

Corticosteroid therapy is not contraindicated in cases of peptic ulcer if it is combined with anti-ulcer treatment.

In patients with a history of ulcer, corticosteroid therapy may be prescribed along with clinical surveillance and, if necessary, after fiberendoscopy.

Cranial trauma on its own, irrespective of the severity, does not represent an indication for the administration of methylprednisolone hemisuccinate. The results of a multicentre, randomised, placebo-controlled study demonstrated an increase in early (at two weeks) and late (at six months) mortality after a cranial trauma in patients receiving methylprednisolone hemisuccinate in comparison with the placebo group. The causes of the excess mortality in the methylprednisolone group have not been established.

Corticosteroid therapy may encourage the appearance of various infectious complications, particularly those caused by bacteria, yeasts and parasites. A major risk is the onset of malignant strongyloidiasis. All subjects arriving from areas where strongyloidiasis is endemic (tropical and subtropical regions, southern Europe) must undergo tests for parasites in stools and receive systematic treatment aimed at eradication prior to corticosteroid therapy.

Active signs of an infection may be masked by corticosteroid therapy.

Before initiating treatment, it is important to rule out any possibility of a visceral focus (especially tuberculous) and to monitor the onset of infectious diseases during the course of treatment.

In cases of earlier tuberculosis, prophylactic antituberculosis treatment is required, if there are appreciable radiological sequelae and if it cannot be confirmed that 6 months of well conducted treatment with rifampicin has been given.

The use of corticosteroid therapy requires particularly appropriate monitoring, especially in the elderly and patients with ulcerative colitis (risk of perforation), diverticulitis, recent intestinal anastomoses, renal impairment, hepatic insufficiency, osteoporosis, or myasthenia gravis.

Oral or injectable corticosteroids could favour the appearance of tendinopathy, or even a rupture of the tendon (exceptional). This risk increases in case of co-prescription with fluoroquinolones and in dialysed patients with secondary hyperparathyroidism or who have undergone a renal transplant.

The attention of sportsmen/women is drawn to the fact that this proprietary medicinal product contains an active substance that might produce a positive reaction in tests carried out during antidoping controls.

This medicinal product contains 2.0 mmol (or 81 mg) sodium per dose. To be taken into consideration by patients on a controlled sodium diet

Precautions for use
The changeover to oral treatment should be initiated as soon as possible.

Water and sodium retention normally occurs and is partially responsible for any increase in blood pressure. The patient's sodium intake must be reduced.

Potassium supplementation is only justified with high dose therapy, prescribed for a long period, or if there is a risk of disturbances of rhythm or combination with a potassium-depleting agent.

When corticosteroid therapy is essential, diabetes and hypertension are not contraindications, although treatment may cause an imbalance in both cases: their management should be re-evaluated.

Patients must avoid contact with subjects suffering from chickenpox or measles.

4.5 Interaction with other medicinal products and other forms of interaction

Inadvisable combinations
- Drugs inducing atypical ventricular tachycardia: astemizole, bepridil, IV erythromycin, halofantrine, pentamidine, sparfloxacin, sultopride, terfenadine, and vincamine.
Atypical ventricular tachycardia (hypokalaemia, bradycardia and a pre-existing long Q-T interval are predisposing factors).
In cases of hypokalaemia, use substances that do not have the disadvantage of giving rise to atypical ventricular tachycardia.

Combinations requiring special precautions for use
- Acetylsalicylic acid by the systemic route (and, by extrapolation, other salicylates)
Reduction in salicylaemia during corticosteroid therapy and risk of salicylate overdosage after its cessation (increased salicylate excretion with corticosteroids).
Adjust the salicylate doses while the combination is being used and after the withdrawal of treatment with corticosteroids.
- **Antiarrhythmic agents inducing atypical ventricular tachycardia** : amiodarone, disopyramide, quinidine-like drugs, and sotalol.
Atypical ventricular tachycardia (hypokalaemia, bradycardia and a pre-existing long Q-T interval are predisposing factors).
Prevention of hypokalaemia and, if necessary, correction: monitor the Q-T interval. If wave bursts occur, do not administer an antiarrhythmic agent (electrical facing).
- **Oral anticoagulants**
Possible impact of corticosteroid therapy on the metabolism of the oral anticoagulant and on that of coagulation factors. Risk of haemorrhage specific to corticosteroid therapy (digestive mucosa, vascular fragility) at high doses or during prolonged treatment for more than 10 days.
When the combination is justified, increase surveillance: laboratory controls after 8 days, and then every 15 days during corticosteroid therapy and following its discontinuation.
- **Other potassium-depleting agents**: potassium-sparing diuretics (alone or in combination), stimulant laxatives, amphotericin B (IV route).
Increased risk of hypokalaemia (additive effect).
Monitor the serum potassium concentration and, if necessary, correct ; particular attention should be paid if digitalis glycosides are used in treatment.
- **Digitalis glycosides**
Hypokalaemia enhances the toxic effects of digitalis glycosides. Monitor the serum potassium concentration and, when appropriate, the ECG.
- **Heparins (parenteral route)**
Aggravation by heparin of the haemorrhagic risk intrinsic to corticosteroid therapy (gastrointestinal mucosa, blood vessel fragility) when administered at high doses or over a prolonged period of more than 10 days.
Such a combination must be justified and monitoring stepped up.
- **Enzyme inducers**:
Antiepileptic drugs: carbamazepine, phenobarbital, phenytoin, primidone, rifampicin.
Reduction in plasma concentrations and efficacy of corticosteroids due to increased hepatic metabolism. The repercussions are of major importance in addisonian and transplant patients.
Clinical and laboratory monitoring, and adjustment of corticosteroid dosage during use of the combination and after withdrawal of the enzyme inducer.
- **Insulin, metformin, and hypoglycemic sulphonylureas**
Elevation in blood glucose, sometimes with ketosis (reduction in carbohydrate tolerance due to corticosteroids). Warn the patient and step up self-monitoring of blood and urine, especially at the start of treatment. Possibly adjust the dosage of antidiabetic during corticosteroid therapy and after its withdrawal.

- **Isoniazid** (described with prednisolone)
Reduction in plasma isoniazid concentrations. Suggested mechanism: increased metabolism of isoniazid in the liver and reduced hepatic metabolism of glucocorticoids.
Clinical and laboratory monitoring.

Combinations to be taken into consideration
- **Antihypertensives**
Reduction in the antihypertensive effect (water and sodium retention due to corticosteroids).
- **Ciclosporin**
Possible increase in plasma ciclosporin and creatinine concentrations.
Proposed mechanism: reduction in hepatic elimination of ciclosporin.
- Fluoroquinolones
Possible increase of the risk of tendinopathy, or even rupture of the tendon (exceptional), especially in patients who receive a long-term corticosteroid therapy.
- **Interferon alfa**
Risk of inhibiting the action of interferon.
- **Attenuated live vaccines**
Risk of generalized, possibly lethal, disease. The risk is increased in subjects who are already immunocompromised by the underlying disease.

Use an inactivated vaccine when available (poliomyelitis).

4.6 Pregnancy and lactation

Pregnancy
A teratogenic effect - which varies according to the species considered - has been found in animal experiments.

The drug crosses the placenta in pregnant women. However, epidemiological studies have failed to detect any risk of malformation related to the administration of corticosteroids during the first trimester of pregnancy.

Slight intrauterine growth retardation may occur when chronic diseases require treatment throughout pregnancy. Neonatal adrenal insufficiency has been observed in rare cases after high-dose corticosteroid therapy.

A period of laboratory and clinical monitoring (weight and urinary output) is justified in neonates.

Consequently, corticosteroids may be prescribed during pregnancy if necessary.

Lactation
Lactation is inadvisable during long-term and high-dose therapy.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Related to parenteral administration:
- Rare cases of anaphylactic reactions have been reported in patients treated with parenteral corticosteroids (see section 4.4).
- Cases of cardiac arrhythmia and/or circulatory collapse and/or cardiac arrest have been reported following the excessively rapid administration of high doses by the intravenous route.
- Tachycardia has sometimes been noted after injection of the product: it is rapidly reversible.
- Episodes of bradycardia occurring during or after the infusion of high doses have been described, independent of the duration or rate of infusion.

Other effects
- Water and electrolyte disturbances: hypokalaemia, metabolic alkalosis, water and sodium retention, hypertension, and congestive heart failure.
- Endocrine and metabolic disorders: iatrogenic Cushing's syndrome, ACTH secretion inertia, occasionally definitive atrophy of the adrenal cortex, reduction in glucose tolerance, revelation of latent diabetes, arrested growth in children, and menstrual irregularities.
- Musculoskeletal disorders: muscular atrophy preceded by muscle weakness (increase in protein catabolism), osteoporosis, pathological fractures, especially compression of vertebrae, and osteochondrosis of the capitular epiphysis of the femur.
- Some rare cases of rupture of the tendon have been described exceptionally, especially when co-prescribed with fluoroquinolones.
- Gastrointestinal disturbances: peptic ulcers, ulceration of the small intestine, gastrointestinal perforations and hemorrhages, and acute pancreatitis have been reported, primarily in children.
- Skin disorders: acne, purpura, ecchymosis, hypertrichosis and delayed healing.
- Neuropsychological disturbances:
  - frequently: euphoria, insomnia and excitation.
  - rarely: acute manic-like episodes, confusional or confusional-oniric states, and convulsions.
  - depressive state upon withdrawal of treatment.
- Ocular disorders: certain forms of glaucoma and cataract.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/
and emailed to the Registration Holder’s Patient Safety Unit at: drugsafety@neopharmgroup.com

4.9 Overdose

There is no specific antidote in cases of massive overdosage: treatment is basically symptomatic.

In a hospital setting, doses ranging up to 30 mg/kg are used for slow I.V. injection (minimum duration = 20 minutes) during short term corticosteroid therapy.

Signs of adrenocortical hyperfunction may possibly occur, as with any high-dose, long-term corticosteroid therapy, particularly disturbances in carbohydrate metabolism, tetany due to hypocalcaemia, cushingoid appearance, and mental excitement.

These disturbances can usually be reversed merely by decreasing the doses or discontinuing treatment.

Methylprednisolone is dialyzable.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: GLUCOCORTICOID - SYSTEMIC USE,
(H. Non sex hormones)
(D. Dermatology)
(M. Locomotive apparatus)

Physiological glucocorticoids (cortisone and hydrocortisone) are essential metabolic hormones. Synthetic corticosteroids, including methylprednisolone, are used mainly for their anti-inflammatory effect. At high doses, they lower the immune response. They have less effect than hydrocortisone on metabolism and sodium retention.

5.2 Pharmacokinetic properties

Methylprednisolone diffuses rapidly, has a half-life of 3.5 hours, is excreted in both urine and bile, is distributed in breast milk and crosses the placenta.

5.3 Preclinical safety data

Not relevant.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium dihydrogen phosphate dihydrate, disodium hydrogen phosphate dodecahydrate, sodium hydroxide.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

After reconstitution the solution should be used immediately

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Vial (type I glass) with a stopper (chlorobutyl). Box of 1,10 or 20.

6.6 Special precautions for disposal and other handling

In order to avoid drilling a hole in the closures, it is recommended that a needle with an outside diameter of 0.8 mm or less be used.

7. MANUFACTURER

Mylan S.A.S., 117 Allée des Parcs, 69800 Saint Priest

8. REGISTRATION HOLDER

Genmedix, 12 Beit Harishonim St., Emek Heffer

9. MARKETING AUTHORISATION NUMBER(S)

125 71 30506 00

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