# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

METHYLPREDNISOLONE VIATRIS 500 MG
METHYLPREDNISOLONE VIATRIS 1 G

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Methylprednisolone Viatris 500 mg:

| | |
|---|---|
| Methylprednisolone hemisuccinate: | 633.50 mg |
| Quantity equivalent to methylprednisolone base: | 500.00 mg |
| | Per vial |

Excipient with known effect
Methylprednisolone Viatris 500 mg contains 41 mg sodium per vial.

Methylprednisolone Viatris 1 g:

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

Excipient with known effect
Methylprednisolone Viatris 1 g contains 81 mg sodium per vial.
For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Lyophilized powder for solution for injection or infusion.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Methylprednisolone Viatris is indicated to treat any condition in which IV corticosteroid treatment is required such as: endocrine disorders, rheumatic disorders, collagen diseases, immune complex diseases, dermatologic diseases, allergic states, ophthalmic diseases, gastrointestinal diseases, respiratory diseases, hematologic disorders, management of neoplastic diseases, edematous states, nervous system disorders and organ transplantation.

### 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 sections 4.4 and 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

Methylprednisolone Viatris is contraindicated:

- in patients who have systemic fungal infections unless specific anti-infective therapy is employed and in cerebral oedema in malaria.
- in patients with known hypersensitivity to methylprednisolone or to any of the excipients listed in section 6.1.
- for use by the intrathecal route of administration.

Administration of live or live attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids.

## 4.4 Special warnings and precautions for use

Immunosuppressant Effects/Increased Susceptibility to Infections
Corticosteroids may increase susceptibility to infection, may mask some signs of infection, and new infections may appear during their use. Suppression of the inflammatory response and immune function increases the susceptibility to fungal, viral and bacterial infections and their severity. The clinical presentation may often be atypical and may reach an advanced stage before being recognised.

Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids.

Chickenpox is of serious concern since this normally minor illness may be fatal in immunosuppressed patients. Patients (or parents of children) without a definite history of chickenpox should be advised to avoid close personal contact with chickenpox or herpes zoster and if exposed they should seek urgent medical attention. Passive immunization with varicella/zoster immunoglobin (VZIG) is needed by exposed non-immune patients who are receiving systemic corticosteroids or who have used them within the previous 3 months; this should be given within 10 days of exposure to chickenpox. If a diagnosis of chickenpox is confirmed, the illness warrants specialist care and urgent treatment. Corticosteroids should not be stopped and the dose may need to be increased.

Exposure to measles should be avoided. Medical advice should be sought immediately if exposure occurs. Prophylaxis with normal intramuscular immunoglobulin may be needed.

Similarly, corticosteroids should be used with great care in patients with known or suspected

parasitic infections such as Strongyloides (threadworm) infestation, which may lead to Strongyloides hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia. Live vaccines should not be given to individuals with impaired immune responsiveness. The antibody response to other vaccines may be diminished.

The use of corticosteroids in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate anti-tuberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.

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

Data from a clinical study conducted to establish the efficacy of methylprednisolone in septic shock, suggest that a higher mortality occurred in subsets of patients who entered the study with elevated serum creatinine levels or who developed a secondary infection after therapy began. Therefore, this product should not be used in the treatment of septic syndrome or septic shock.

The role of corticosteroids in septic shock has been controversial, with early studies reporting both beneficial and detrimental effects. More recently, supplemental corticosteroids have been suggested to be beneficial in patients with established septic shock who exhibit adrenal insufficiency. However, their routine use in septic shock is not recommended. A systematic review of short-course, high-dose corticosteroids did not support their use. However, meta-analyses, and a review suggest that longer courses (5-11 days) of low-dose corticosteroids might reduce mortality, especially in patients with vasopressor-dependent septic shock.

Immune System Effects

Allergic reactions may occur. Rarely skin reactions and anaphylactic/anaphylactoid reactions have been reported following parenteral methylprednisolone therapy. Physicians using the drug should be prepared to deal with such a possibility. Appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of drug allergy.

Endocrine Effects

In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during and after the stressful situation is indicated.

Pharmacologic doses of corticosteroids administered for prolonged periods may result in hypothalamic-pituitary-adrenal (HPA) suppression (secondary adrenocortical insufficiency). The degree and duration of adrenocortical insufficiency produced is variable among patients and depends on the dose, frequency, time of administration, and duration of glucocorticoid therapy. This effect may be minimized by use of alternate-day therapy.

In addition, acute adrenal insufficiency leading to a fatal outcome may occur if glucocorticoids are withdrawn abruptly.

In patients who have received more than physiological doses of systemic corticosteroids (approximately 6 mg methylprednisolone) for greater than 3 weeks, withdrawal should not be abrupt.

Drug-induced secondary adrenocortical insufficiency may therefore be minimized by gradual reduction of dosage. How dose reduction should be carried out depends largely on whether the disease is likely to relapse as the dose of systemic corticosteroids is reduced. Clinical assessment of disease activity may be needed during withdrawal. If the disease is unlikely to relapse on withdrawal of systemic corticosteroids, but there is uncertainty about HPA suppression, the dose of systemic corticosteroid may be reduced rapidly to physiological doses. Once a daily dose of 6 mg methylprednisolone is reached, dose reduction should be slower to allow the HPA-axis to recover.

Abrupt withdrawal of systemic corticosteroid treatment, which has continued up to 3 weeks is appropriate if it considered that the disease is unlikely to relapse. Abrupt withdrawal of doses up to 32 mg daily of methylprednisolone for 3 weeks is unlikely to lead to clinically relevant HPA-axis suppression, in the majority of patients. In the following patient groups, gradual withdrawal of systemic corticosteroid therapy should be *considered* even after courses lasting 3 weeks or less:

- Patients who have had repeated courses of systemic corticosteroids, particularly if taken for greater than 3 weeks.
- When a short course has been prescribed within one year of cessation of long-term therapy (months or years).
- Patients who may have reasons for adrenocortical insufficiency other than exogenous corticosteroid therapy.
- Patients receiving doses of systemic corticosteroid greater than 32 mg daily of methylprednisolone.
- Patients repeatedly taking doses in the evening.

This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted.

A steroid "withdrawal syndrome," seemingly unrelated to adrenocortical insufficiency, may also occur following abrupt discontinuance of glucocorticoids. This syndrome includes symptoms such as: anorexia, nausea, vomiting, lethargy, headache, fever, joint pain, desquamation, myalgia, weight loss, and/or hypotension. These effects are thought to be due to the sudden change in glucocorticoid concentration rather than to low corticosteroid levels.

Because glucocorticoids can produce or aggravate Cushing's syndrome, glucocorticoids should be avoided in patients with Cushing's disease.

There is an enhanced effect of corticosteroids on patients with hypothyroidism. Frequent patient monitoring is necessary in patients with hypothyroidism.

Metabolism and Nutrition

Frequent patient monitoring is necessary in patients with diabetes mellitus (or a family history of diabetes). Corticosteroids, including methylprednisolone, can increase blood glucose, worsen pre-existing diabetes, and predispose those on long-term corticosteroid therapy to diabetes mellitus.

Psychiatric Effects

Patients and/or carers should be warned that potentially severe psychiatric adverse reactions may occur with systemic steroids (see section 4.8). Symptoms typically emerge within a few days or weeks of starting treatment. Risks may be higher with high doses/systemic exposure

(see also section 4.5), although dose levels do not allow prediction of the onset, type, severity or duration of reactions. Most reactions recover after either dose reduction or withdrawal, although specific treatment may be necessary. Patients/carers should be encouraged to seek medical advice if worrying psychological symptoms develop, especially if depressed mood or suicidal ideation is suspected. Patients/carers should be alert to possible psychiatric disturbances that may occur either during or immediately after dose tapering/withdrawal of systemic steroids, although such reactions have been reported infrequently.

Particular care is required when considering the use of systemic corticosteroids in patients with existing or previous history of severe affective disorders in themselves or in their first degree relatives. These would include depressive or manic-depressive illness and previous steroid psychosis.

Frequent patient monitoring is necessary in patients with existing or previous history of severe affective disorders (especially previous steroid psychosis).

Nervous System Effects
Corticosteroids should be used with caution in patients with seizure disorders. Frequent patient monitoring is necessary in patients with epilepsy.

Corticosteroids should be used with caution in patients with myasthenia gravis. (Also see myopathy statement in Musculoskeletal Effects section). Frequent patient monitoring is necessary in patients with myasthenia gravis.

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

There have been reports of epidural lipomatosis in patients taking corticosteroids, typically with long-term use at high doses.

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

Frequent patient monitoring is necessary in patients with glaucoma (or a family history of glaucoma) and in patients with ocular herpes simplex, for fear of corneal perforation.

Prolonged use of corticosteroids may produce posterior subcapsular cataracts and nuclear cataracts (particularly in children), exophthalmos, or increased intraocular pressure, which may result in glaucoma with possible damage to the optic nerves. Establishment of secondary fungal and viral infections of the eye may also be enhanced in patients receiving glucocorticoids.

Cardiac Effects
Adverse effects of glucocorticoids on the cardiovascular system, such as dyslipidemia and hypertension, may predispose treated patients with existing cardiovascular risk factors to additional cardiovascular effects, if high doses and prolonged courses are used. Accordingly, corticosteroids should be employed judiciously in such patients and attention should be paid to risk modification and additional cardiac monitoring if needed. Low dose and alternate day therapy may reduce the incidence of complications in corticosteroid therapy.

There have been a few reports of cardiac arrhythmias and/or circulatory collapse and/or cardiac arrest associated with the rapid intravenous administration of large doses of methylprednisolone (greater than 500 mg administered over a period of less than 10 minutes). Bradycardia has been reported during or after the administration of large doses of methylprednisolone , and may be unrelated to the speed and duration of infusion.

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

Care should be taken for patients receiving cardioactive drugs such as digoxin because of steroid induced electrolyte disturbance/potassium loss (see section 4.8).

Frequent patient monitoring is necessary in patients with congestive heart failure or recent myocardial infarction (myocardial rupture has been reported).

Vascular Effects
Steroids should be used with caution in patients with hypertension. Frequent patient monitoring is necessary.

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

Gastrointestinal Effects
High doses of corticosteroids may produce acute pancreatitis.

There is no universal agreement on whether corticosteroids per se are responsible for peptic ulcers encountered during therapy; however, glucocorticoid therapy may mask the symptoms of peptic ulcer so that perforation or haemorrhage may occur without significant pain. Glucocorticoid therapy may mask peritonitis or other signs or symptoms associated with gastrointestinal disorders such as perforation, obstruction or pancreatitis.

In combination with NSAIDs, the risk of developing gastrointestinal ulcers is increased.

Particular care is required when considering the use of systemic corticosteroids in patients with the following conditions and frequent patient monitoring is necessary:
Ulcerative colitis
Perforation, Abscess or other pyogenic infections
Diverticulitis
Fresh intestinal anastomoses
Peptic ulceration

Hepatobiliary Effects
Drug induced liver injury including acute hepatitis or liver enzyme increase can result from cyclical pulsed IV methylprednisolone (usually at initial dose ≥ 1 g/day). Rare cases of hepatotoxicity have been reported. The time to onset can be several weeks or longer. In the majority of case reports resolution of the adverse events has been observed after treatment was discontinued. Therefore, appropriate monitoring is required.

Musculoskeletal Effects
Particular care is required when considering the use of systemic corticosteroids in patients with myasthenia gravis or osteoporosis (post-menopausal females are particularly at risk) and frequent patient monitoring is necessary.

Osteoporosis is a common but infrequently recognized adverse effect associated with a long-term use of large doses of glucocorticoid.

Renal and urinary disorders
Caution is required in patients with systemic sclerosis because an increased incidence of scleroderma renal crisis has been observed with corticosteroids, including methylprednisolone. Blood pressure and renal function (s-creatinine) should therefore be routinely checked. When renal crisis is suspected, blood pressure should be carefully controlled.

Particular care is required when considering the use of systemic corticosteroids in patients with renal insufficiency and frequent patient monitoring is necessary.

Investigations
Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

Injury, poisoning and procedural complications
Systemic corticosteroids are not indicated for, and therefore should not be used to treat, traumatic brain injury, a multicenter study revealed an increased mortality at 2 weeks and 6 months after injury in patients administered methylprednisolone compared to placebo. A causal association with methylprednisolone treatment has not been established.

Other
Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment as to whether daily or intermittent therapy should be used.

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects (see section 4.5).

The lowest possible dose of corticosteroid should be used to control the condition under treatment and when reduction in dosage is possible, the reduction should be gradual.

Aspirin and non-steroidal anti-inflammatory agents should be used cautiously in conjunction with corticosteroids.

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

In post marketing experience tumour lysis syndrome (TLS) has been reported in patients with malignancies, including haematological malignancies and solid tumours, following the use of systemic corticosteroids alone or in combination with other chemotherapeutic agents. Patients at high risk of TLS, such as patients with tumours that have a high proliferative rate, high tumour burden and high sensitivity to cytotoxic agents, should be monitored closely and appropriate precautions should be taken.

Severe medical events have been reported in association with the intrathecal/epidural routes of administration. There have been reports of epidural lipomatosis in patients taking corticosteroids, typically with long-term use at high doses.

Paediatric population:

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed. Growth may be suppressed in children receiving long-term, daily, divided-dose glucocorticoid therapy and use of such regimen should be restricted to the most urgent indications. Alternate-day glucocorticoid therapy usually avoids or minimizes this side effect.

Infants and children on prolonged corticosteroid therapy are at special risk from raised intracranial pressure.
High doses of corticosteroids may produce pancreatitis in children.

Hypertrophic cardiomyopathy may develop after administration of methylprednisolone to prematurely born infants, therefore appropriate diagnostic evaluation and monitoring of cardiac function and structure should be performed.

Excipient information

Methylprednisolone Viatris 500 mg contains 41 mg sodium per vial, equivalent to 2.05% of the WHO recommended maximum daily intake of 2 g sodium for an adult.
Methylprednisolone Viatris 1 g contains 81 mg sodium per vial, equivalent to 4.05% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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

Methylprednisolone is a cytochrome P450 enzyme (CYP) substrate and is mainly metabolized by the CYP3A4 enzyme. CYP3A4 is the dominant enzyme of the most abundant CYP subfamily in the liver of adult humans. It catalyzes 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 drugs) have been shown to alter glucocorticoid metabolism by induction (up-regulation) or inhibition of the CYP3A4 enzyme.

CYP3A4 INHIBITORS - Drugs that inhibit CYP3A4 activity generally decrease hepatic clearance and increase the plasma concentration of CYP3A4 substrate medications, such as methylprednisolone. In the presence of a CYP3A4 inhibitor, the dose of methylprednisolone may need to be titrated to avoid steroid toxicity.

CYP3A4 INDUCERS - Drugs that induce CYP3A4 activity generally increase hepatic clearance, resulting in decreased plasma concentration of medications that are substrates for CYP3A4. Co-administration may require an increase in methylprednisolone dosage to achieve the desired result.

CYP3A4 SUBSTRATES - In the presence of another CYP3A4 substrate, the hepatic clearance of methylprednisolone may be affected, with corresponding dosage adjustments required. It is possible that adverse events associated with the use of either drug alone may be more likely to occur with co-administration.

NON-CYP3A4-MEDIATED EFFECTS – Other interactions and effects that occur with

methylprednisolone are described in Table 2 below.

Table 2 provides a list and descriptions of the most common and/or clinically important drug interactions or effects with methylprednisolone.

Table 2. *Important drug or substance interactions/effects with methylprednisolone*

| **Drug Class or Type - DRUG or SUBSTANCE** | **Interaction** | **Effect** |
|---|---|---|
| Macrolide Antibacterial<br>- TROLEANDOMYCIN<br><br>Antibacterial<br>- ISONIAZID<br><br>- GRAPEFRUIT JUICE | CYP3A4 INHIBITOR | CYP3A4 INHIBITOR.<br>An increase in the plasma concentration of methylprednisolone may occur. The dose of methylprednisolone may need to be titrated to avoid steroid toxicity<br>In addition, there is a potential effect of methylprednisolone to increase the acetylation rate and clearance of isoniazid. |
| Antibiotic, Antitubercular<br>- RIFAMPIN<br><br>Anticonvulsants<br>- PHENOBARBITAL<br>- PHENYTOIN | CYP3A4 INDUCER | CYP3A4 INDUCER<br>A decrease in the plasma concentration of methylprednisolone may occur.<br>Co-administration may require an increase in methylprednisolone dosage to achieve the desired result. |
| Antiemetic<br>- APREPITANT<br>- FOSAPREPITANT<br><br>Antifungal<br>- ITRACONAZOLE<br>- KETOCONAZOLE<br><br>Antivirals<br>- HIV-PROTEASE INHIBITORS<br>Pharmacokinetic enhancers<br>- COBICISTAT<br><br>Calcium Channel Blocker<br>- DILTIAZEM<br><br>Contraceptives (oral)<br>- ETHINYLESTRADIOL / NORETHISTERONE<br><br>Immunosuppressant<br>- CICLOSPORIN<br><br>Macrolide Antibacterial<br>- CLARITHROMYCIN<br>- ERYTHROMYCIN | CYP3A4 INHIBITORS (and SUBSTRATES) | CYP3A4 INHIBITORS (and SUBSTRATES)<br>The hepatic clearance of methylprednisolone may be inhibited or induced, resulting in an increase or decrease in the plasma concentration of methylprednisolone. A corresponding dosage adjustment may be required. It is possible that adverse events associated with the use of either drug alone may be more likely to occur with administration<br>1) Protease inhibitors, such as indinavir and ritonavir, may increase plasma concentrations of corticosteroids.<br>2) Corticosteroids may induce the metabolism of HIV protease inhibitors resulting in reduced plasma concentrations.<br><br>Ciclosporin<br>1) Mutual inhibition of metabolism occurs with concurrent use of ciclosprin and methylprednisolone, which may increase the plasma concentrations of either or both drugs. Therefore, it is possible that adverse events associated with the use of either drug alone may be more likely to occur upon co-administration.<br>2) Convulsions have been reported with concurrent use of methylprednisolone and |

| | | |
|---|---|---|
| | | ciclosporin. |
| Anticonvulsants<br>- CARBAMAZEPINE | CYP3A4 INDUCER (and SUBSTRATE) | CYP3A4 INDUCER (and SUBSTRATE)<br>The hepatic clearance of methylprednisolone may be inhibited or induced, resulting in an increase or decrease in the plasma concentration of methylprednisolone. A corresponding dosage adjustment may be required. It is possible that adverse events associated with the use of either drug alone may be more likely to occur with administration |
| Immunosuppressant<br>- CYCLOPHOSPHAMIDE<br>- TACROLIMUS | CYP3A4 SUBSTRATES | CYP3A4 SUBSTRATES<br>The hepatic clearance of methylprednisolone may be inhibited or induced, resulting in an increase or decrease in the plasma concentration of methylprednisolone. A corresponding dosage adjustment may be required. It is possible that adverse events associated with the use of either drug alone may be more likely to occur with administration |
| Anticoagulants (oral) | Non-CYP3A4 mediated effects | The effect of methylprednisolone on oral anticoagulants is variable. There are reports of enhanced as well as diminished effects of anticoagulants when given concurrently with corticosteroids. Therefore, coagulation indices should be monitored to maintain the desired anticoagulant effects. |
| Anticholinergics<br>- NEUROMUSCULAR BLOCKERS | | Corticosteroids may influence the effect of anticholinergics.<br>1) An acute myopathy has been reported with the concomitant use of high doses of corticosteroids and anticholinergics, such as neuromuscular blocking drugs. (See section 4.4, Musculoskeletal, for additional information.)<br>2) 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. |
| Anticholinesterases | | Steroids may reduce the effects of anticholinesterases in myasthenia gravis. |
| Anti-diabetics | | Because corticosteroids may increase blood glucose concentrations, dosage adjustments of anti-diabetic agents may be required. |

| | | |
|---|---|---|
| Aromatase inhibitors<br>- AMINOGLUTETHIMIDE | | Aminoglutethimide-induced adrenal suppression may exacerbate endocrine changes caused by prolonged glucocorticoid treatment. |
| NSAIDs (non-steroidal anti-inflammatory drugs)<br>- high-dose ASPIRIN (acetylsalicylic acid) | | 1) There may be increased incidence of gastrointestinal bleeding and ulceration when corticosteroids are given with NSAIDs.<br>2) Methylprednisolone may increase the clearance of high-dose aspirin, which can lead to decreased salicylate serum levels. Discontinuation of methylprednisolone treatment can lead to raised salicylate serum levels, which could lead to an increased risk of salicylate toxicity. |
| Potassium depleting agents | | When corticosteroids are administered concomitantly with potassium depleting agents (e.g. diuretics) patients should be observed closely for development of hypokalaemia.<br>Corticosteroids antagonize the diuretic effect of diuretics.<br>There is also an increased risk of hypokalaemia with concurrent use of corticosteroids with amphotericin B, xanthines, or beta2 agonists. |

Corticosteroids antagonize the hypotensive effect of all antihypertensives.

There is an increased risk of hypokalaemia when corticosteroids are given with cardiac glycosides.

The effects of corticosteroids may be reduced for 3-4 days after mifepristone.

Incompatibilities
To avoid compatibility and stability problems, it is recommended that methylprednisolone be administered separately from other compounds that are administered via the IV route of administration. Drugs that are physically incompatible in solution with methylprednisolone include allopurinol sodium, doxapram hydrochloride, tigecycline, diltiazem hydrochloride, calcium gluconate, vecuronium bromide, rocuronium bromide, cisatracurium besylate, glycopyrrolate and propofol (see section 6.2 for additional information).

## 4.6 Fertility, pregnancy and lactation

Fertility
Corticosteroids have been shown to impair fertility in animal studies (see section 5.3). In women treatment with corticosteroids can lead to menstrual irregularities.

Pregnancy
The ability of corticosteroids to cross the placenta varies between individual drugs, however, methylprednisolone does cross the placenta.

Administration of corticosteroids to pregnant animals can cause abnormalities of foetal development including cleft palate, intra-uterine growth retardation and affects on brain growth and development. There is no evidence that corticosteroids result in an increased incidence of congenital abnormalities, such as cleft palate in man, however, when administered for long periods or repeatedly during pregnancy, corticosteroids may increase the risk of intra-uterine growth retardation. Hypoadrenalism may, in theory, occur in the neonate following pre-natal exposure to corticosteroids but usually resolves spontaneously following birth and is rarely clinically important. Infants born to mothers, who have received substantial doses of corticosteroids during pregnancy must be carefully observed and evaluated for signs of adrenal insufficiency. As with all drugs, corticosteroids should only be prescribed when the benefits to the mother and child outweigh the risks. When corticosteroids are essential, however, patients with normal pregnancies may be treated as though they were in the non-gravid state.

Since adequate human reproductive studies have not been done with methylprednisolone, this medicinal product should be used during pregnancy only after a careful assessment of the benefit-risk ratio to the mother and fetus.

In humans, the risk of low birth weight appears to be dose related and may be minimized by administering lower corticosteroid doses.

Cataracts have been observed in infants born to mothers undergoing long-term treatment with corticosteroids during pregnancy.

Breast-feeding
Corticosteroids are excreted in small amounts in breast milk, however, doses of up to 40 mg daily of methylprednisolone are unlikely to cause systemic effects in the infant. This medicinal product should be used during breast feeding only after a careful assessment of the benefit-risk ratio to the mother and infant.

## 4.7 Effects on ability to drive and use machines

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

## 4.8 Undesirable effects

The following adverse reactions have been reported with the following routes of administration:
Intrathecal/Epidural: Arachnoiditis, functional gastrointestinal disorder/bladder dysfunction, headache, meningitis, paraparesis/paraplegia, seizure and sensory disturbances

Under normal circumstances methylprednisolone therapy would be considered as short-term. However, the possibility of side-effects attributable to corticosteroid therapy should be recognised, particularly when high-dose therapy is being used (see section 4.4). Such side-effects include:

| **MedDRA** *System Organ Class* | **Frequency†** | **Undesirable Effects** |
|---|---|---|

| | | |
|---|---|---|
| ***Infections and infestations*** | ***Not Known*** | Infection (including increased susceptibility and severity of infections with suppression of clinical symptoms and signs); Opportunistic infection; Recurrence of dormant tuberculosis (see section 4.4), Peritonitis[#] |
| ***Neoplasms benign, malignant and unspecified (including cysts and polyps)*** | ***Not Known*** | Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy. Discontinuation of corticosteroids may result in clinical remission. |

| | | |
|---|---|---|
| ***Blood and lymphatic system disorders*** | ***Not Known*** | Leukocytosis |
| ***Immune system disorders*** | ***Not Known*** | Drug hypersensitivity (Anaphylactic reaction Anaphylactoid reaction) |
| ***Endocrine disorders*** | ***Not Known*** | Cushingoid; Hypothalamic pituitary adrenal axis suppression , Steroid withdrawal syndrome (including, fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and loss of weight). |
| ***Metabolism and nutrition disorders*** | ***Not Known*** | Metabolic acidosis; Sodium retention; Fluid retention; Glucose tolerance impaired; Alkalosis hypokalaemic; Dyslipidemia, Increased insulin requirements (or oral hypoglycemic agents in diabetics); Lipomatosis, Increased appetite (which may result in weight increase); Epidural lipomatosis |
| ***Psychiatric disorders*** | ***Not Known*** | A wide range of psychiatric reactions including affective disorders (such as irritable, euphoric, depressed and labile mood drug dependence and suicidal thoughts), psychotic reactions (including mania, delusions, hallucinations and schizophrenia), behavioural disturbances, irritability, anxiety, sleep disturbances, and cognitive dysfunction including confusion and amnesia have been reported for all corticosteroids. Reactions may occur in both adults and children. In adults, the frequency of severe reactions was estimated to be 5%-6%. Psychological effects have been reported on withdrawal of corticosteroids; the frequency is unknown. |
| ***Nervous system disorders*** | ***Not Known*** | Increased intracranial pressure with Papilloedema [Benign intracranial hypertension]; Seizure; Amnesia; Cognitive disorder; Dizziness; Headache |

| | | |
|---|---|---|
| ***Eye disorders*** | ***Rare*** | Vision blurred (see also section 4.4). |
| | ***Not Known*** | Posterior subcapsular cataracts; Exophthalmos; Glaucoma; Papilloedema with possible damage to the optic nerve; Corneal or scleral thinning; Exacerbation of ophthalmic viral or fungal disease; Chorioretinopathy. |

| | | |
|---|---|---|
| ***Ear and labyrinth disorders*** | ***Not Known*** | Vertigo |
| ***Cardiac disorders*** | ***Not Known*** | Congestive heart failure in susceptible patients, Arrhythmia |
| ***Vascular disorders*** | ***Not Known*** | Hypertension; Hypotension; Thrombotic events, Flushing |
| ***Respiratory, thoracic and mediastinal disorders*** | ***Not Known*** | Hiccups; Pulmonary embolism. |
| ***Gastrointestinal disorders*** | ***Not Known*** | Peptic ulcer (with possible peptic ulcer perforation and peptic ulcer haemorrhage); Gastric haemorrhage; Intestinal perforation; Pancreatitis; Ulcerative oesophagitis; Oesophagitis; Oesophageal candidiasis; Abdominal pain; Abdominal distension; Diarrhoea; Dyspepsia; Nausea; Vomiting; Bad taste in mouth may occur especially with rapid administration |
| ***Hepatobiliary disorders*** | ***Not Known*** | Hepatitis†; Increase of liver enzymes (e.g alanine aminotransferase increased (ALT, SGPT), aspartate aminotransferase increased (AST, SGOT)). |
| ***Skin and subcutaneous tissue disorders*** | ***Not Known*** | Ecchymosis; Skin atrophy (thin fragile skin); Acne; Angioedema; Petechiae; Skin striae; Telangiectasia; Skin hypopigmentation or hyperpigmentation; Hirsutism; Rash; Erythema; Pruritus; Urticaria; Hyperhidrosis |
| ***Musculoskeletal and connective tissue disorders*** | ***Not Known*** | Growth retardation; Osteoporosis; Muscular weakness; Osteonecrosis; Pathological fracture; Muscle atrophy; Myopathy; Neuropathic arthropathy; Arthralgia; Myalgia |
| ***Reproductive system and breast disorders*** | ***Not Known*** | Irregular menstruation; Amenorrhoea |
| ***General disorders and administration site conditions*** | ***Not Known*** | Impaired wound healing; Oedema peripheral; Injection site reaction; Fatigue; Malaise; Withdrawal symptoms - Too rapid a reduction of corticosteroid dosage following prolonged treatment can lead to acute adrenal insufficiency, hypotension and death. However, this is more applicable to corticosteroids with an indication where continuous therapy is given (see Section 4.4) |

| | | |
|---|---|---|
| ***Investigations*** | ***Not Known*** | Intraocular pressure increased; Carbohydrate tolerance decreased; Blood potassium decreased (potassium loss); Urine calcium increased; Blood alkaline phosphatase increased; Blood urea increased; Suppression of reactions to skin tests |
| ***Injury, poisoning and procedural complications*** | ***Not Known*** | Tendon rupture (particularly of the Achilles tendon); Spinal compression fracture (vertebral compression fractures) |

† Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Not known (frequency cannot be estimated from the available data)
† Hepatitis has been 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. 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/

### 4.9 Overdose

There is no clinical syndrome of acute overdosage with corticosteroids. Reports of acute toxicity and/or death following overdosage of corticosteroids are rare. In the event of overdosage, no specific antidote is available; treatment is supportive and symptomatic. Methylprednisolone is dialysable. Following chronic overdosage the possibility of adrenal suppression should be guarded against by gradual diminution of dose levels over a period of time. In such event the patient may require to be supported during any further stressful episode.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Glucocorticoids, ATC code: H02AB04

Methylprednisolone is a corticosteroid with an anti-inflammatory activity at least five times that of hydrocortisone.
An enhanced separation of glucocorticoid and mineralocorticoid effect results in a reduced incidence of sodium and water retention.

### 5.2 Pharmacokinetic properties

Methylprednisolone pharmacokinetics is linear, independent of route of administration.

Distribution:
Methylprednisolone is widely distributed into the tissues, crosses the blood-brain barrier, and is secreted in breast milk. Its apparent volume of distribution is approximately 1.4 L/kg. The plasma protein binding of methylprednisolone in humans is approximately 77%.

Biotransformation:
Methylprednisolone is extensively bound to plasma proteins, mainly to globulin and less so to

albumin. Only unbound corticosteroid has pharmacological effects or is metabolised. Metabolism occurs in the liver and to a lesser extent in the kidney. In humans, methylprednisolone is metabolized in the liver to inactive metabolites; the major ones are 20α-hydroxymethylprednisolone and 20β-hydroxymethylprednisolone.

Metabolism in the liver occurs primarily via the CYP3A4. (For a list of drug interactions based on CYP3A4-mediated metabolism, see section 4.5).

Methylprednisolone, like many CYP3A4 substrates, may also be a substrate for the ATP-binding cassette (ABC) transport protein p-glycoprotein, influencing tissue distribution and interactions with other medicines.

Elimination:
Metabolites are excreted in the urine.

The mean elimination half-life for total methylprednisolone is in the range of 1.8 to 5.2 hours. Total clearance is approximately 5 to 6 mL/min/kg. Mean elimination half-life ranges from 2.4 to 3.5 hours in normal healthy adults and appears to be independent of the route of administration.

Total body clearance following intravenous injection of methylprednisolone to healthy adult volunteers is approximately 15-16 L/hour.

## 5.3 Preclinical safety data

Based on conventional studies of safety pharmacology and repeated dose toxicity, no unexpected hazards were identified. The toxicities seen in the repeated-dose studies were those expected to occur with continued exposure to exogenous adrenocortical steroids.
Mutagenic potential:
Methylprednisolone has not been formally evaluated for genotoxicity. Studies using structurally related analogues of methylprednisolone showed no evidence of a potential for genetic and chromosome mutations in limited studies in bacteria and mammalian cells.

Carcinogenic potential:
Methylprednisolone has not been formally evaluated in rodent carcinogenicity studies. Variable results have been obtained with other glucocorticoids tested for carcinogenicity in mice and rats. However, published data indicate that several related glucocorticoids including budesonide, prednisolone, and triamcinolone acetonide can increase the incidence of hepatocellular adenomas and carcinomas after oral administration in drinking water to male rats. These tumorigenic effects occurred at doses which were less than the typical clinical doses on a $mg/m^2$ basis. The clinical relevance of these findings is unknown.

Reproductive toxicity:
Methylprednisolone has not been evaluated in animal fertility studies. Corticosteroids have been shown to reduce fertility when administered to rats. Adverse effects on fertility in male rats administered corticosterone were observed and were reversible. Decreased weights and microscopic changes in prostate and seminal vesicles were observed. The numbers of implantations and live fetuses were reduced and these effects were not present following mating at the end of the recovery period.

An increased frequency of cleft palate was observed among the offspring of mice treated during pregnancy with methylprednisolone in doses similar to those typically used for oral therapy in humans.

An increased frequency of cardiovascular defects and decreased body weight were observed among the offspring of pregnant rats treated with methylprednisolone in a dose that was similar to that used for oral therapy in humans but was toxic to the mothers. In contrast, no teratogenic effect was noted in rats with doses <1-18 times those typically used for oral therapy in humans in another study. High frequencies of foetal death and a variety of central nervous system and skeletal anomalies were reported in the offspring of pregnant rabbits treated with methylprednisolone in doses less than those used in humans. The relevance of these findings to the risk of malformations in human infants born to mothers treated with methylprednisolone in pregnancy is unknown. Safety margins for the reported teratogenic effects are unknown.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Disodium hydrogen phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate, 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

Store below 25°C.

### 6.5 Nature and contents of container

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

Not all pack sizes may be marketed.

### 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.

Reconstitution:

Methylprednisolone Viatris 500 mg
The powder should be reconstituted with 7.8 ml Water for Injection.
To be used immediately.

Methylprednisolone Viatris 1 g
The powder should be reconstituted with 15.6 ml Water for Injection.
To be used immediately.

## 7. MARKETING AUTHORISATION HOLDER

Dexcel Ltd
1 Dexcel street, Or Akiva, 3060000, Israel

## 8. MARKETING AUTHORISATION NUMBER(S)

METHYLPREDNISOLONE VIATRIS 500 MG: 125 72 30505 00
METHYLPREDNISOLONE VIATRIS 1 G: 125 71 30506 00

Revised in September 2024 according to MOH guidelines.