פייזר פי אף אי פרמצבטיקה ישראל בע"מ
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אוגוסט 2017

רופא/ה, רוקח/ת נכבד/ה,
ברצוננו להודיעך על עדכון בעלון לרופא של
Solu-Medrol 40mg/ml; Solu-Medrol 125mg; Solu-Medrol 500mg; Solu-Medrol 1000mg
קו תחתי משמעו תוספת טקסט, קו חוצה משמעו מחיקת טקסט, הדגשה משמעה החמרה.

<u>הרכב וחוזק:</u>
Methylprednisolone (as methylprednisolone sodium succinate) 40mg; 125 mg; 500mg; 1000mg

<u>התוויה:</u>
Solu Medrol is indicated to treat any condition in which IM or 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.

<u>להלן העדכונים העיקריים בעלון לרופא:</u>

Contraindications
Solu-Medrol is contraindicated:
- Solu-Medrol 40mg/ml: in patients with a known hypersensitivity to cow's milk or its components, or other dairy products, because it contains trace amounts of milk ingredients.
- ~~for use by the epidural route of administration.~~

Special warnings and precautions for use
~~Infections with any pathogen including viral, bacterial, fungal, protozoan or helminthic organisms, in any location in the body, may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents that affect cellular or humoral immunity, or neutrophil function. These infections may be mild, but can be severe and at times fatal. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases.~~

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.

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<u>Data from a clinical study conducted to establish the efficacy of Solu-Medrol 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.</u>
…
~~Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered to patients receiving immunosuppressive doses of corticosteroids; however, the response to such vaccines may be diminished. Indicated immunization procedures may be undertaken in patients receiving non-immunosuppressive doses of corticosteroids.~~

~~Blood and Lymphatic System~~
~~Aspirin and nonsteroidal anti-inflammatory agents should be used cautiously in conjunction with corticosteroids.~~

Immune System Effects
Allergic reactions may occur. ~~Because rare instances of skin reactions and~~

~~anaphylactic/anaphylactoid reactions have occurred in patients receiving corticosteroid therapy.~~ Rarely skin reactions and anaphylactic/anaphylactoid reactions have been reported following parenteral Solu-Medrol 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.

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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. ~~Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.~~

Nervous System Effects

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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.

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Vascular Effects

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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

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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.

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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.

~~An acute myopathy has been reported with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (eg, myasthenia gravis), or in patients receiving concomitant therapy with anticholinergics, such as neuromuscular blocking drugs (eg, pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevations of creatine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.~~

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Injury, poisoning and procedural complications

~~Corticosteroids should not be used for the management of head injury or stroke because it is unlikely to be of benefit and may even be harmful.~~

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 sodium succinate compared to placebo. A causal association with methylprednisolone sodium succinate treatment has not been established.

Other

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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).

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Paediatric population:

~~The preservative benzyl alcohol has been associated with serious adverse events, including the "gasping syndrome", and death in pediatric patients. Although normal therapeutic doses of this product ordinarily deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the "gasping syndrome", the minimum amount of benzyl alcohol at which toxicity may occur is not known. The risk of benzyl alcohol toxicity depends on the quantity administered and the hepatic capacity to detoxify the chemical. Premature and low-birth weight infants may be more likely to develop toxicity.~~

~~Use in the elderly: The common adverse effects of systemic corticosteroids may be associated with more serious consequences in old age, especially osteoporosis, hypertension, hypokalaemia, diabetes, susceptibility to infection and thinning of the skin. Caution is recommended with prolonged corticosteroid treatment in the elderly due to a potential increase risk for osteoporosis, as well as increased risk for fluid retention with possible resultant hypertension. Close clinical supervision is required to avoid life-threatening reactions.~~

Interaction with other medicinal products and other forms of interaction

CYP3A4 INHIBITORS (and SUBSTRATES): Pharmacokinetic enhancers: COBICISTAT…
Effect: Corticosteroids may induce the metabolism of HIV protease inhibitors resulting in reduced Plasma concentrations….

Non-CYP3A4-mediated effects effect:
Anticholinesterases: Steroids may reduce the effects of anticholinesterases in myasthenia gravis.
Aromatase inhibitors: Aminoglutethimide - induced adrenal suppression may ~~impede~~ exacerbate endocrine changes caused by prolonged glucocorticoid treatment.

Fertility, pregnancy and lactation

Pregnancy

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Since adequate human reproductive studies have not been done with methylprednisolone sodium succinate, 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.

~~There are no known effects of corticosteroids on labor and delivery.~~
~~Benzyl alcohol can cross the placenta. (See Section 4.4 Special warnings and precautions for use).~~

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.

~~Corticosteroids distributed into breast milk may suppress growth and interfere with endogenous glucocorticoid production in nursing infants. Since adequate reproductive studies have not been performed in humans with glucocorticoids, these drugs should be administered to nursing mothers only if the benefits of therapy are judged to outweigh the potential risks to the infant.~~

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

Infections and infestations: ~~***Common***~~ ***Not Known:*** Infection (including increased susceptibility and severity of infections with suppression of clinical symptoms and signs)
Endocrine disorders: ~~***Common***~~ ***Not Known*****:** Cushingoid

Metabolism and nutrition disorders: ~~***Common***~~ ***Not Known*****:** Metabolic acidosis; Sodium retention; Fluid retention; ~~Negative nitrogen balance (dueto protein catabolism);~~ Epidural lipomatosis
Psychiatric disorders: ~~***Common***~~ ***Not Known:*** A wide range of psychiatric reactions including affective disorders (such as irritable, euphoric, depressed and labile mood ~~psychological~~ drug dependence and suicidal thoughts), psychotic reactions (including mania, delusions, hallucinations and ~~aggravation of~~ schizophrenia), behavioural disturbances, irritability, anxiety, sleep disturbances, and cognitive dysfunction including confusion and amnesia have been reported for all corticosteroids. Reactions ~~are common and~~ 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.
Eye disorders: ~~***Common:***~~ ***Not Known:*** Posterior subcapsular cataracts…Chorioretinopathy.
Vascular disorders: ~~***Common:***~~ ***Not Known:*** Hypertension
Respiratory, thoracic and mediastinal disorders: Not Known**:** Pulmonary embolism.
Gastrointestinal disorders: ~~***Common:***~~ ***Not Known:*** Peptic ulcer (with possible peptic ulcer perforation and peptic ulcer haemorrhage);
Hepatobiliary disorders:Not Known: Hepatitis†; Increase of liver enzymes.
† Hepatitis has been reported with IV administration (see section 4.4).
Skin and subcutaneous tissue disorders: ~~***Common***~~ ***Not Known:*** Ecchymosis; Skin atrophy (thin fragile skin); Acne
Musculoskeletal and connective tissue disorders: ~~***Common***~~ ***Not Known*****:** Growth retardation (in children); Osteoporosis; Muscular weakness…
General disorders and administration site conditions: ~~***Common***~~ ***Not Known:*** Impaired wound healing;
Investigations: ~~***Common***~~ ***Not Known:*** Blood potassium decreased (potassium loss), ~~Alanine aminotransferase increased~~

העלון לרופא נשלח למשרד הבריאות לצורך פרסומו במאגר התרופות שבאתר משרד הבריאות:
http://www.health.gov.il/units/pharmacy/trufot/index.asp

לחילופין, לקבלת עלון מלא מודפס ניתן לפנות לחברת פייזר פי אף אי פרמצבטיקה ישראל בע"מ
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בברכה,

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