רופא/ה, רוקח/ת נכבד/ה, יולי 2022

חברת טבע מודיעה על עדכון בעלון לרופא של התכשיר:

Gentamicin Teva 80 mg/2ml

Solution for I.M. or I.V Injection

גנטמיצין טבע 80 מ"ג/2 מ"ל

תמיסה להזרקה לתוך השריר או לתוך הוריד

כל אמפולה של 2 מ"ל מכילה: Gentamicin (as sulfate) 80 mg

עדכון בעלון לרופא

<u>התוויה כפי שאושרה בתעודת הרישום:</u>

Gentamicin is indicated in bacteremia, urinary tract infections, endocarditis, chest infections and other serious systemic infections due to confirmed or expected bacteria that are susceptible to gentamicin, in adults and children, including neonates.

<u>ברצוננו להודיע שהעלון לרופא עודכן. להלן העדכונים העיקריים בלבד (תוספת מידע מסומנת באדום, החמרות מסומנות על רקע צהוב ומידע שהורד מסומן ~~באדום עם קו חוצה~~):</u>

4.4 Special warnings and precautions for use

<u>Ototoxicity and nephrotoxicity</u>

Ototoxicity has been reported following the use of aminoglycosides, including gentamicin. Symptoms include loss of balance and hearing loss, which may be irreversible (see section 4.8). Important risk factors include renal impairment, high doses, prolonged duration of treatment and age (neonates/infants and possibly the elderly). Due to the potential for ototoxicity and nephrotoxicity, monitoring of vestibule, cochlea and renal function is recommended before, during and shortly after treatment (see section 4.8). Serum levels are determined so as to avoid peak concentrations above 10mg/l and troughs above 1 mg/l when administering gentamicin once daily and 2mg/l when administering gentamicin twice daily.

As there is some evidence that risk of both ototoxicity and nephrotoxicity is related to the level of total exposure, duration of therapy should be the shortest possible compatible with clinical recovery. In some patients with impaired renal function there has been a transient rise in blood-urea-nitrogen which has usually reverted to normal during or following cessation of therapy. It is important to adjust the frequency of dosage according to the degree of renal function.

There have been observed cases of an increased risk of ototoxicity with aminoglycosides administered to patients with mitochondrial mutations, particularly the m.1555A>G mutation, including cases where the patient's aminoglycoside serum levels were within the recommended

range. Some cases were associated with a maternal history of deafness and/or mitochondrial mutation. Mitochondrial mutations are rare, and the penetrance of this observed effect is unknown.

In cases of significant obesity gentamicin serum concentrations should be closely monitored and a reduction in dose should be considered. To avoid adverse events, continuous monitoring (before, during and after treatment) of hepatic and laboratory parameters is also recommended.

~~*Pregnancy and lactation*~~

Gentamicin should only be used in pregnancy ~~and during lactation~~if considered essential by the physician ~~only after careful benefit risk assessment~~ (see section 4.6).

Gentamicin should be used with care in conditions characterised by muscular weakness.

Superinfection

Treatment with gentamicin may produce an excessive growth of drug-resistant micro-organisms. If this happens, an appropriate treatment should be initiated.

~~In patients with advanced renal impairment or with pre-existing inner ear deafness, gentamicin should be used only if its use is considered essential by the physician. The frequency or dose of administration should be reduced in patients with impaired renal function (see section 4.2).~~

~~*Renal impairment*~~

~~Renal impairment such as restriction of glomerular filtration is observed in approximately 10% of patients treated with gentamicin and is usually reversible. The most important risk factors are high total dose, long duration of therapy, raised serum level (high trough level); in addition, other potential risk factors are age, hypovolaemia and shock.~~

~~Clinical signs of renal damage are: proteinuria, cylindruria, haematuria, oliguria, raised creatinine and urea concentrations in serum. In isolated cases, acute renal failure may occur. (See also section 4.8)~~

~~*Neuromuscular disorders*~~

~~Since gentamicin has neuromuscular blocking properties, particular caution should be exercised in patients with pre- existing neuromuscular diseases (e.g. Parkinson's disease). Particularly careful monitoring is mandatory. (See also section 4.8.)~~

~~Neuromuscular blockade and respiratory paralysis have been reported from administration of aminoglycosides to patients who have received curare-type muscle relaxants during anaesthesia. These patients should also be monitored very carefully. (See also section 4.8.)~~

~~*Effect on vestibulocochlear nerve*~~

~~Damage to the vestibulocochlear nerve (eighth cranial nerve), whereby both balance and hearing may be affected, is possible. Vestibular damage is the most common ototoxic reaction. Hearing loss is manifested initially by diminution of high-tone acuity and is usually irreversible. Important risk factors are pre-existing renal impairment or a history of damage to the eighth cranial nerve; in addition, the risk increases in proportion to the level of the total and daily dose or by association with potentially ototoxic substances. Symptoms of ototoxic effects are: dizziness, ringing/roaring in the ears (tinnitus), vertigo and less common hearing loss.~~

~~With gentamicin the vestibular mechanism may be affected if trough levels of 2 µg/ml are exceeded. This is usually reversible if observed promptly and the dose adjusted. (See also section 4.8)~~

~~*Antibiotic-associated diarrhoea*~~ Pseudomembranous colitis

~~Antibiotic-associated~~ Diarrhoea and pseudomembranous colitis have been ~~reported~~ observed when gentamicin is combined with other antibiotics.~~with the use of gentamicin.~~ These diagnoses should be considered in every ~~any~~ patient that develops diarrhoea during or immediately ~~shortly~~ after treatment. Gentamicin should be discontinued if the patient suffers severe ~~and/or bloody~~ diarrhoea and/or bloody diarrhoea ~~occurs~~ during treatment and an appropriate treatment should be initiated. ~~therapy instituted.~~ Drugs that inhibit peristalsis should not be administered ~~must not be given~~ (see section 4.8).

Severe subcutaneous adverse reactions (SCARs)

Serious skin reactions including Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported in association with gentamicin treatment. Patients should be informed about the signs and symptoms of serious skin manifestations and monitored closely. Treatment should be discontinued at the first appearance of skin rash, mucosal lesions or any other sign of skin hypersensitivity.

~~Once daily dosing of gentamicin in elderly patients:~~

~~There is limited experience with once daily dosing of gentamicin in elderly patients. Once daily dosing of gentamicin may not be suitable and therefore, close monitoring is warranted in these patients.~~

[…]

~~*Cross-allergenicity/ resistance*~~

~~Cross resistance and hypersensitivity to aminoglycosides may occur.~~

~~*Monitoring*~~

~~To avoid adverse events, continuous monitoring (before, during and after treatment) of renal function (serum creatinin, creatinin clearance), control of function of vestibule and cochlea as well as hepatic and laboratory parameters is recommended.~~

~~In order to reduce the risk of nephrotoxicity and ototoxicity, the following instructions should be considered:~~

~~– Regular assessment of auditory, vestibular and renal function is particularly necessary in patients with additional risk factors. Impaired hepatic function or auditory function, bacteraemia and fever have been reported to increase the risk of ototoxicity. Volume depletion or hypotension and liver disease have been reported as additional risk factors for nephrotoxicity.~~

~~– Monitoring of renal function before, during and after treatment.~~

~~– Dosage strictly according to creatinine clearance (or serum creatinine concentration). In patients with impaired renal function, the dosage must be adjusted according to renal performance (see section 4.2).~~

~~– In patients with impaired renal function additionally receiving gentamicin locally (inhalation, intratracheal, instillation), the amount of gentamicin absorbed after local administration must also be taken into account for dose adjustment of systemic treatment.~~

~~– Monitoring of serum gentamicin concentrations during therapy in order to avoid that peak levels exceed 10 µg/ml (toxic threshold for the cochleo-vestibular system) with conventional multiple daily dosing or trough levels exceed 2 µg/ml (see section 4.2) when administrating gentamicin twice daily and 1 mg/l for a once daily dosing.~~

~~– In patients with pre-existing inner ear damage (hearing impairment or balance function impairment), or where treatment is long-term, additional monitoring of the balance function and hearing is required.~~

~~– Prolonged treatment should be avoided. If possible, the duration of therapy should be limited to 7 – 10 days (see section 4.2).~~

~~– Avoid therapy with aminoglycosides immediately subsequent to previous aminoglycoside treatment; if possible, there should be an interval of 7 – 14 days between treatments.~~

~~– If possible, avoid concurrent administration of other potentially ototoxic and nephrotoxic substances. If this is unavoidable, particular careful monitoring of renal function is indicated (see section 4.5).~~

~~– Ensure adequate hydration and urine production.~~

4.5 Interaction with other medicinal products and other forms of interaction

~~**Muscle relaxants and ether**~~

~~The neuromuscular blocking activity of aminoglycosides is enhanced by ether and muscle relaxants.~~

~~If gentamicin is administered during or immediately after surgery, the neuromuscular blockade may be enhanced and prolonged if non-depolarising muscle relaxants are used. These interactions may cause neuromuscular blockage and respiratory paralysis. Because of the increased risk, such patients should be monitored with particular care.~~

~~Injection with calcium chloride may reverse the neuromuscular blockade due to aminoglycosides but should be undertaken with caution.~~

~~**Methoxyflurane anaesthesia**~~

~~Aminoglycosides may increase the kidney damaging effect of methoxyflurane. When used concurrently, extremely severe nephropathies are possible. The anaesthetist should be made aware of the use of aminoglycosides before a surgical procedure~~.

Potentially nephrotoxic or ototoxic drugs Ototoxicity and nephrotoxicity

Concurrent administration of gentamicin and other potentially ototoxic or nephrotoxic drugs should be avoided. ~~whenever possible. Where co- administration is considered necessary, because of the increased risk of undesired effects, careful monitoring is required of patients being treated concurrently or sequentially with potentially nephrotoxic or ototoxic drugs such as:~~Potent diuretics such as etacrynic acid and furosemide are expected to enhance the risk of ototoxicity whilst amphotericin B, cisplatin and ciclosporin are potential enhancers of nephrotoxicity.

Any potential nephrotoxicity of cephalosporins, and in particular cephaloridine, may also be increased in the presence of gentamicin. Consequently, if this combination is used monitoring of kidney function is advised.~~Antibacterials: some cephalosporins notably cephalotin and cephaloridine, colistin, vancomycin, viomycin, other aminoglycosides such as streptomycin. Antifungals: amphotericin B~~

~~- Loop diuretics such as ethacrynic acid and frusemide~~

~~- Cytotoxics: cisplatin. It must be noted that the nephrotoxicity of gentamicin can be increased even 3 to 4 weeks after these substances are administered.~~

~~- Anti suppressant: ciclosporin~~

~~**Other antibiotics**~~

~~A reduction in gentamicin serum half-life has been reported in patients with severe renal impairment receiving carbenicillin concomitantly with gentamicin.~~

~~**Indometacin**~~

~~Indometacin possibly increases plasma concentrations of gentamicin in neonates.~~

~~**Oral anticoagulants**~~

~~Concurrent use with oral anticoagulants may increase the hypothrombinanaemic effect.~~

~~**Bisphosphonates**~~

~~Concurrent use of bisphosphonates may increase the risk of hypocalcaemia.~~

~~**Cholinergics**~~

~~Antagonism of effect may occur with concomitant administration of gentamicin with either neostigmine or pyridostigmine.~~

~~Concurrent use of botulinum toxin and gentamicin may increase the risk of toxicity due to enhanced neuromuscular block.~~

Neuromuscular blockade

Neuromuscular blockade and respiratory paralysis have been reported from administration of aminoglycosides to patients who have received curare-type muscle relaxants during anaesthesia. Concomitant use of gentamicin with drugs with neuromuscular blocking effects, such as botulinum toxin, may increase the risk of toxicity due to enhanced neuromuscular block.

Aminoglycosides such as gentamicin can also act as neuromuscular blockers and may therefore antagonise the effects of neostigmine or pyridostigmine.

The following combinations with gentamicin may require dose adjustment:

•Concomitant use of indomethacin possibly increases plasma concentrations of gentamicin in neonates

•Concomitant use with oral anticoagulants may decrease thrombin levels and increase the risk of bleeding.

• Concomitant use of bisphosphonates with gentamicin may increase the risk of hypocalcaemia

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited ~~no adequate~~ data from the use of aminoglycosides, including gentamicin, ~~gentamicin~~ in pregnant women. ~~Studies in animals have shown reproductive toxicity (see section 5.3).~~ Gentamicin crosses the placenta, and there is a risk of ototoxicity (vestibulocochlear nerve damage) and/or renal damage in the fetus, as seen in animal studies (see section 5.3). Gentamicin should not be used in pregnancy, except ~~unless~~ in case of life-threatening situations where expected ~~indication and if the~~ benefits outweighs possible ~~the~~ risk.

In such case, maternal serum gentamicin concentration monitoring is recommended (see section 4.2). ~~of exposition to gentamicin during pregnancy~~, Monitoring of hearing and renal function of the infants ~~newborn~~ is also recommended.

Breast-feeding

Gentamicin is excreted in human breast milk and was detected in low concentrations in the serum of breast-fed children, except in cases where the mucous membrane of the infant's stomach and intestines is severely eroded.

In cases of suspected severe mucosal erosion, if the infant is breast-fed during gentamicin treatment, it is recommended to monitor the serum concentration of gentamicin in the infant (see section 4.2). Animal and human data suggest that if the serum gentamicin concentration in the infant exceeds 1 µg/ml either breast-feeding or the gentamicin therapy may need to be

discontinued, under medical supervision. The following effects of gentamicin on the infant's normal gastrointestinal flora are possible and it is recommended to monitor the infant for possible effects such as diarrhoea, candidiasis and bloody stools.

~~A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from gentamicin therapy. Diarrhoea and fungus infection of the mucous membranes could occur in the breast-fed infant, so that nursing might have to be discontinued. The possibility of sensitisation should be borne in mind.~~

4.8 Undesirable effects

~~Under certain conditions gentamicin shows ototoxic and/or nephrotoxic effects. Renal impairment is commonly observed in patients treated with gentamicin and is usually reversible upon withdrawal of the drug. In most cases nephrotoxicity is associated with an excessively high dosage or prolonged treatment, pre-existing renal abnormalities or associated with other substances reported to be nephrotoxic.~~

~~The adverse reactions considered at least possibly related to treatment are listed below by body system organ class and absolute frequency. Frequencies are defined as:~~

The following CIOMS frequency rating is used, when applicable:

very common (≥1/10);

common (≥1/100 to <1/10);

uncommon (≥1/1000 to <1/100);

rare (≥1/10 000 to <1/1000);

very rare (<1/10 000) ;

not known (frequency cannot be estimated from the available data).

Infections and infestations:

Not known: antibiotic-associated colitis (including pseudomembranous colitis), superinfection (caused by gentamicin-resistant bacteria)

Blood and lymphatic system disorders:

Not known: anaemia, blood dyscrasias

Immune system disorders:

Not known: hypersensitivity (see section 4.4), anaphylaxis/anaphylactic reaction (including anaphylactic shock)

Metabolism and nutrition disorders:

Not known: hypomagnesaemia on prolonged therapy

Psychiatric disorders:

Not known: depression, hallucinations, confusion

Nervous system disorders:

Not known: central neuropathy (including convulsions, lethargy, encephalopathy), peripheral neuropathy

Ear and labyrinth disorders:

Not known: vestibular damage, transitory hearing loss, irreversible hearing loss, deafness, particularly after exposure to ototoxic drugs or in the presence of renal dysfunction (see section 4.4).

Gastrointestinal disorders:

Very common: vomiting

Not known: stomatitis, nausea

Hepatobiliary disorders:

Not known: abnormal liver function, transaminases increased

Skin and subcutaneous tissue disorders:

Not known: Stevens-Johnson syndrome, toxic epidermal necrosis, rash, purpura, urticaria, pruritus

Renal and urinary disorders:

Very rare: acute renal failure, Fanconi-like syndrome in patients treated with a prolonged course of high dose

Not known: nephrotoxicity (usually reversible) has been reported.

5.3 Preclinical safety data

~~**Chronic toxicity**~~

~~In studies on chronic toxicity (i.m. application) carried out on various animal species, nephrotoxic and ototoxic effects were observed at high dosages.~~

~~**Mutagenic and carcinogenic potential**~~

~~Gentamicin was not mutagenic in in vitro and in vivo tests. There are no long-term studies on animals on the carcinogenic potential of gentamicin.~~

Reproductive and development toxicity

~~There is a potential risk of inner ear and renal damage to the fetus as was observed for the class of aminoglycoside antibiotics. Fetal renal abnormalities have been documented in rats and guinea pigs after administration of gentamicin to the dams.~~

The limited non-clinical literature mentions that prenatal or postnatal administration of gentamicin to rodents and guinea pigs produces developmental toxicity of the kidney and/or inner ear in fetuses and offspring.