הודעה על החמרה (מידע בטיחות) בעלון לרופא

**תאריך 14/2/2016**

**שם התכשיר באנגלית ומספר הרישום Zithromax I.V. 124-14-30374-00/01**

**שם בעל הרישום Pfizer PFE Pharmaceuticals Israel Ltd**

טופס זה מיועד לפרוט ההחמרות בלבד!

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| **ההחמרות המבוקשות** | | |
| **פרק בעלון** | **טקסט נוכחי** | **טקסט חדש** |
| **Contraindications** |  | ZITHROMAX I.V. is contraindicated in patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of azithromycin. |
| **Warnings and Precautions** | As with erythromycin and other macrolides, rare serious allergic reactions, including angioedema and anaphylaxis (rarely fatal), and dermatologic reactions including Stevens Johnson Syndrome and toxic epidermal necrolysis (rarely fatal),have been reported.  Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.  If an allergic reaction occurs, the drug should be discontinued and appropriate therapy should be instituted. Physicians should be aware that reappearance of the allergic symptoms may occur when symptomatic therapy is discontinued.  Providers should consider the risk of QT prolongation which can be fatal when weighing the risks and benefits of azithromycin for at-risk groups including:   * Patients with congenital or documented QT prolongation a history of torsades de pointes, bradyarrhythmias or uncompensated heart failure * Patients currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of classes IA ( quinidine,procainamide) and III(dofetilide,aminodarone,sotalol); antipsychotic agents; antidepressants; and fluoroquinolones * Patients with electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesemia * Patients with clinically relevant bradycardia, cardiac arrhythmia or cardiac insufficiency * Elderly patients: elderly patients may be more susceptible to drug-associated effects on the QT interval | Serious allergic reactions, including angioedema, anaphylaxis, and dermatologic reactions including Stevens-Johnson Syndrome, toxic epidermal necrolysis, and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) have been reported in patients on azithromycin therapy.  Fatalities have been reported. Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms recurred soon thereafter in some patients without further azithromycin exposure. These patients required prolonged periods of observation and symptomatic treatment. The relationship of these episodes to the long tissue half‑life of azithromycin and subsequent prolonged exposure to antigen is unknown at present. 5.3 Infantile hypertrophic pyloric stenosis (IHPS) Following the use of azithromycin in neonates (treatment up to 42 days of life), infantile hypertrophic pyloric stenosis (IHPS) has been reported. Parents and caregivers should be informed to contact their physician if vomiting or irritability with feeding occurs.  Cases of torsades de pointes have been spontaneously reported during postmarketing surveillance in patients receiving azithromycin. Providers should consider the risk of QT prolongation, which can be fatal when weighing the risks and benefits of azithromycin for at-risk groups including:   * patients with known prolongation of the QT interval, a history of torsades de pointes, congenital long QT syndrome, bradyarrhythmias or uncompensated heart failure * patients on drugs known to prolong the QT interval * patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents.   Elderly patients may be more susceptible to drug-associated effects on the QT interval.  If CDAD is suspected or confirmed, ongoing antibacterial use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.   5.6 Exacerbation of Myasthenia Gravis Exacerbations of symptoms of myasthenia gravis and new onset of myasthenic syndrome have been reported in patients receiving azitrhromycin therapy. 5 7 Infusion Site Reactions ZITHROMAX I.V. for injection should be reconstituted and diluted as directed and administered as an intravenous infusion over not less than 60 minutes. *[see Dosage and Administration (2)]*  Local IV site reactions have been reported with the intravenous administration of azithromycin. The incidence and severity of these reactions were the same when 500 mg azithromycin was given over 1 hour (2 mg/mL as 250 mL infusion) or over 3 hr (1 mg/mL as 500 mL infusion) *[see Adverse Reactions (6)].* All volunteers who received infusate concentrations above 2.0 mg/mL experienced local IV site reactions and, therefore, higher concentrations should be avoided. 5.8 Development of Drug-Resistant Bacteria Prescribing ZITHROMAX I.V. in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. |
| **Adverse events** | Gastrointestinal Disorders: Nausea, vomiting, diarrhea, loose stools, abdominal discomfort (pain/cramps), and flatulence.  Skin and Subcutaneous Tissue Disorders: Allergic reactions including rash and angioedema.  Gastrointestinal Disorders: Nausea, vomiting, diarrhea, loose stools, abdominal discomfort (pain/cramps), and flatulence.  Gastrointestinal Disorders: Vomiting/diarrhea (rarely resulting in dehydration), dyspepsia, constipation, digestive disorders, anorexia, pseudomembranous colitis, pancreatitis, and rare reports of tongue discoloration  Skin and Subcutaneous Tissue Disorders: Allergic reactions including pruritus, rash, photosensitivity, edema, urticaria, and angioedema. Rarely, serious skin reactions including erythema multiforme, Stevens‑Johnson syndrome, and toxic epidermal necrolysis have been reported. | Clinical adverse reactions leading to discontinuations from these studies were gastrointestinal (abdominal pain, nausea, vomiting, diarrhea), and rashes; laboratory side effects leading to discontinuation were increases in transaminase levels and/or alkaline phosphatase levels.  Overall, the most common adverse reactions associated with treatment in adult patients who received ZITHROMAX I.V. in studies of community-acquired pneumonia were related to the gastrointestinal system with diarrhea/loose stools (4.3%), nausea (3.9%), abdominal pain (2.7%), and vomiting (1.4%) being the most frequently reported.  Approximately 12% of patients experienced a side effect related to the intravenous infusion; most common were pain at the injection site (6.5%) and local inflammation (3.1%).  The most common adverse reactions associated with treatment in adult women who received ZITHROMAX I.V. in trials of pelvic inflammatory disease were related to the gastrointestinal system. Diarrhea (8.5%) and nausea (6.6%) were most commonly reported, followed by vaginitis (2.8%), abdominal pain (1.9%), anorexia (1.9%), rash and pruritus (1.9%). When azithromycin was co-administered with metronidazole in these trials, a higher proportion of women experienced adverse reactions of nausea (10.3%), abdominal pain (3.7%), vomiting (2.8%), infusion site reaction, stomatitis, dizziness, or dyspnea (all at 1.9%).  Adverse reactions that occurred with a frequency of 1% or less included the following:  *Gastrointestinal:*Dyspepsia, flatulence, mucositis, oral moniliasis, and gastritis.  *Nervous system:* Headache, somnolence.  *Allergic:* Bronchospasm.  *Special senses:* Taste perversion.  *Gastrointestinal:* Anorexia, constipation, dyspepsia, flatulence, vomiting/diarrhea, pseudomembranous colitis, pancreatitis, oral candidiasis, pyloric stenosis, and reports of tongue discoloration.  *Skin/appendages:* Pruritus, serious skin reactions including, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, and DRESS. 6.3 Laboratory Abnormalities Significant abnormalities (irrespective of drug relationship) occurring during the clinical trials were reported as follows:   * elevated ALT (SGPT), AST (SGOT), creatinine (4 to 6%) * elevated LDH, bilirubin (1 to 3%) * leukopenia, neutropenia, decreased platelet count, and elevated serum alkaline phosphatase (less than 1%)   When follow‑up was provided, changes in laboratory tests appeared to be reversible.  In multiple‑dose clinical trials involving more than 750 patients treated with ZITHROMAX I.V., less than 2% of patients discontinued azithromycin therapy because of treatment‑related liver enzyme abnormalities. |
| **Drug Interactions** | Co-administration of azithromycin (1200 mg) and nelfinavir at steady state (750mg three times daily) resulted in a 100% increase azithromycin absorption and bioavailability. There was no significant effect upon the rate of absorption or the rate of clearance. The clinical consequences of this interaction are unknown, caution should be exercised when prescribing azithromycin to patients tanking nelfinavir.  In a pharmacokinetic interaction study, azithromycin did not alter the anticoagulant effect of a single 15‑mg dose of warfarin administered to healthy volunteers. There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to coadministration of azithromycin and coumarin‑type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when azithromycin is used in patients receiving coumarin-type oral anticoagulants. | Co-administration of nelfinavir at steady-state with a single oral dose of azithromycin resulted in increased azithromycin serum concentrations. Although a dose adjustment of azithromycin is not recommended when administered in combination with nelfinavir, close monitoring for known adverse reactions of azithromycin, such as liver enzyme abnormalities and hearing impairment, is warranted.  Spontaneous post-marketing reports suggest that concomitant administration of azithromycin may potentiate the effects of oral anticoagulants such as warfarin, although the prothrombin time was not affected in the dedicated drug interaction study with azithromycin and warfarin. Prothrombin times should be carefully monitored while patients are receiving azithromycin and oral anticoagulants concomitantly.  Interactions with the following drugs listed below have not been reported in clinical trials with azithromycin; however, no specific drug interaction studies have been performed to evaluate potential drug‑drug interaction. However, drug interactions have been observed with other macrolide products. Until further data are developed regarding drug interactions when digoxin or phenytoin are used with azithromycin careful monitoring of patients is advised. |
| **Pregnancy, fertility and lactation** |  | Pregnancy Category B  Caution should be exercised when azithromycin is administered to a nursing woman. |
| **Pediatric Use** | The safety and efficacy of intravenous azithromycin for the treatment of infections in children has not been established. | Safety and effectiveness of azithromycin for injection in children or adolescents under 16 years have not been established. In controlled clinical studies, azithromycin has been administered to pediatric patients (age 6 months to 16 years) by the oral route. |
| **Geriatric Use** |  | ZITHROMAX I.V. contains 114 mg (4.96 mEq) of sodium per vial. At the usual recommended doses, patients would receive 114 mg (4.96 mEq) of sodium. The geriatric population may respond with a blunted natriuresis to salt loading. The total sodium content from dietary and non-dietary sources may be clinically important with regard to such diseases as congestive heart failure. |

**מצ"ב העלון שבו מסומנים ההחמרות המבוקשות על רקע צהוב.**

שינויים שאינם בגדר החמרות סומנו (בעלון) בצבע שונה (טקסט ירוק). יש לסמן רק תוכן מהותי ולא שינויים במיקום הטקסט.

**הועבר בדואר אלקטרוני בתאריך 14/2/2016**

כל השינויים עולים בקנה אחד עם תנאי הרישום (תעודת הרישום, תעודת האיכות וטופס פרטי התכשיר העדכני).

כל הכתוב בהצעת העלון, תואם את תנאי הרישום.

קיים עלון לצרכן והוא מעודכן בהתאם.

אסמכתא לבקשה: USPI המאושר בארצות הברית מ- 12/2015

**האסמכתא מצ"ב**

השינוי הנ"ל אושר על ידי רשויות הבריאות ב ארצות הברית

אני, הרוקח הממונה של חברת Pfizer PFE Pharmaceuticals Israel Ltd מצהיר בזה כי אין שינויים נוספים, מלבד אלה שסומנו בהצעת העלון.

אני מצהיר כי השינויים אינם יוצרים סתירה פנימית במידע בעלון.

עלון זה לא מטופל במקביל במסגרת אחרת (כגון: עדכון עלון במסגרת בקשה לתוספת התוויה, החמרה וכו'). במידה וקיים טיפול במקביל במסגרת אחרת – יש לציין זאת.

**הוגש בעבר עלון לבדיקתכם בתאריך 06/2015 , עם זאת, שימו לב כי העלון המוגש הוא המעודכן ביותר.**

חתימת הרוקח הממונה (שם וחתימה): \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_