הודעה על החמרה (מידע בטיחות) בעלון לרופא (מעודכן 05.2013)

תאריך **28.07.2015**

שם תכשיר באנגלית **JEVTANA**

מספר רישום 145-23-33286-

שם בעל הרישום **Sanofi-Aventis Israel ltd**

טופס זה מיועד לפרוט ההחמרות בלבד !

פרטים על השינוי/ים המבוקש/ים

פרק בעלון	טקסט נוכחי	טקסט חדש
2.2 DOSE MODIFICATIONS		**מצוין רק המידע שהתווסף ומהווה החמרה.** **Table 1: Recommended Dosage Modifications for Adverse Reactions in Patients Treated with JEVTANA** **Toxicity** / **Dosage Modification** Prolonged grade ≥ 3 neutropenia (greater than 1 week) despite appropriate medication including G-CSF — Delay treatment until neutrophil count is > 1,500 cells/mm^3, then reduce dosage of JEVTANA to 20 mg/m^2. Use G-CSF for secondary prophylaxis. Febrile neutropenia or neutropenic infection — Delay treatment until improvement or resolution, and until neutrophil count is > 1,500 cells/mm^3, then reduce dosage of JEVTANA to 20 mg/m^2. Use G-CSF for secondary prophylaxis. Grade ≥ 3 diarrhoea or persisting diarrhoea despite appropriate medication, fluid and electrolyte replacement — Delay treatment until improvement or resolution, then reduce dosage of JEVTANA to 20 mg/m^2 Grade 2 peripheral neuropathy — Delay treatment until improvement or resolution, then reduce dosage of JEVTANA to 20 mg/m^2. Grade ≥3 peripheral neuropathy — Discontinue JEVTANA Discontinue JEVTANA treatment if a patient continues to experience any of these reactions at 20 mg/m^2. **2.3 Dose Modifications for Hepatic Impairment** • Mild hepatic impairment (total bilirubin > 1 to ≤ 1.5 x Upper Limit of Normal (ULN) or AST >1.5 x ULN): Reduce JEVTANA starting dose to 20 mg/m^2. • Moderate hepatic impairment (total bilirubin > 1.5 to ≤ 3 x ULN and AST = any): Reduce JEVTANA starting dose to 15 mg/m2 based on tolerability data in these patients; however, the efficacy of this dose is unknown. • Severe hepatic impairment (total bilirubin > 3 X ULN): Cabazitaxel is contraindicated in patients with severe hepatic impairment [see Warning and Precautions (5.6) and Clinical Pharmacology (12.3)].

2.4 Dose Modifications for Use with Strong CYP3A Inhibitors **2.3 Dose Modifications for Drug Interactions** **Strong CYP3A inhibitors** Concomitant drugs that are strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) may increase plasma concentrations of cabazitaxel. Avoid the coadministration of JEVTANA with these drugs. If patients require co-administration of a strong CYP3A inhibitor, consider a 25% JEVTANA dose reduction *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.		
מצוין רק המידע שהתווסף ומהווה החמרה, למידע מלא עבור סעיף זה יש לעיין בעלון. • *severe hepatic impairment (total bilirubin > 3 x ULN)*		4. CONTRAINDICATIONS

מצוין רק המידע שהתווסף ומהווה החמרה. למידע מלא עבור סעיף זה יש לבדוק את העלון לרופא. 5.1 Bone marrow suppression Bone marrow suppression manifested as neutropenia, anemia, thrombocytopenia and/or pancytopenia may occur. Neutropenic deaths have been reported. In the randomized trial, five patients (1.3%) experienced fatal infectious adverse events (sepsis or septic shock). All had grade 4 neutropenia and one had febrile neutropenia. One additional patient's death was attributed to neutropenia without a documented infection. Grade 3-4 neutropenia has been observed in 82% of patients treated with JEVTANA in the randomized trial. …….. Caution is recommended in patients with hemoglobin < 10 g/dl. …… *5.6 Hepatic impairment* JEVTANA is contraindicated in patients with severe hepatic impairment (total bilirubin > 3 x ULN) (see Contraindications (4)). Dose should be reduced for patients with mild (total bilirubin >1 to ≤1.5 x ULN or AST >1.5 x ULN) hepatic impairment and moderate (total bilirubin > 1.5 to ≤ 3.0 x ULN and any AST) hepatic impairment, based on tolerability data in these patients [see Dosage and Administration (2.3) and Use in Specific Populations (8.7)]. Administration of cabazitaxel to patients with mild and moderate hepatic impairment should be undertaken with caution and close monitoring of safety. …… 5.7 Embryo-Fetal Toxicity JEVTANA is not indicated for use in female patients. ……		5. WARNINGS AND PRECAUTIONS
מצוין רק המידע שהתווסף ומהווה החמרה. למידע מלא עבור סעיף זה יש לבדוק את העלון לרופא. **7.1 Drugs That May Increase Cabazitaxel Plasma Concentrations** **CYP3A4 Inhibitors**: Cabazitaxel is primarily metabolized through CYP3A [see Clinical Pharmacology (12.3 Strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole) increases concentrations of cabazitaxel. Avoid the co-administration of Jevtana with strong CYP3A inhibitors . **If patients require co-administration of a strong CYP3A inhibitor consider 25% Jevtana dose reduction** (see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)).		7. DRUG INTERACTIONS
תת סעיף 8.7 נמחק, והמידע הועבר לתת סעיף 2.3 **מצוין רק המידע שהתווסף ומהווה החמרה. למידע מלא עבור סעיף זה יש לבדוק את העלון לרופא.** **8.1 Pregnancy** Pregnancy category D. See 'Warnings and Precautions' section. JEVTANA is not indicated for use in female patients. **8.4 Geriatric Use** Of the 371 patients with prostate cancer treated with JEVTANA every three weeks plus prednisone, 240 patients (64.7%) were 65 years of age and over, while 70 patients (18.9%) were 75 years of age and over. No overall differences in effectiveness were observed between patients ≥ 65 years of age and younger patients. Elderly patients (≥ 65 years of age) may be more likely to experience certain adverse reactions. The incidence of death due to causes other than disease progression within 30 days of the last cabazitaxel dose were higher in patients who were 65 years of age or greater compared to younger patients [see Warnings and		8.USE IN SPECIFIC POPULATIONS

Precautions (5.5)]. The incidence of grade 3-4 neutropenia and febrile neutropenia were higher in patients who were 65 years of age or greater compared to younger patients. …… ***8.5 Renal impairment*** No dose adjustment is necessary in patients with renal impairment not requiring hemodialysis. Patients presenting end-stage renal disease (creatinine clearance CLCR <15 mL/min/1.73m2), should be monitored carefully during treatment (see Clinical Pharmacology 11.3) ***8.6 Hepatic impairment*** Cabazitaxel is extensively metabolized by the liver. Patients with mild hepatic impairment (total bilirubin >1 to ≤1.5 x Upper Limit of Normal (ULN) or AST >1.5 x ULN), should have Jevtana dose reduced to 20 mg/m2. Administration of cabazitaxel to patients with mild hepatic impairment should be undertaken with caution and close monitoring of safety(see Clinical Pharmacology 11.3) The maximum tolerated dose in patients with moderate hepatic impairment (total bilirubin >1.5 to ≤3.0 x ULN and AST any) was 15 mg/m2, however, the efficacy at this dose level was unknown. Jevtana is contraindicated in patients with severe hepatic impairment (total bilirubin > 3x ULN) [see Contraindications (4)].		

Renal Impairment Cabazitaxel is minimally excreted via the kidney. A population pharmacokinetic analysis carried out in 170 patients including 14 patients with moderate renal impairment (30 mL/min ≤ CLcr < 50 mL/min) and 59 patients with mild renal impairment (50 mL/min ≤ CLcr < 80 mL/min) showed that mild to moderate renal impairment did not have meaningful effects on the pharmacokinetics of cabazitaxel. This was confirmed by a dedicated comparative pharmacokinetic study in patients with solid tumors with normal renal function (n=8, CLCR > 80 mL/min/1.73m^2), or moderate (n=8, 30 mL/min/1.73m^2 ≤ CLCR < 50 mL/min/1.73m^2) and severe (n=9, CLCR < 30 mL/min/1.73m^2) renal impairment, who received several cycles of cabazitaxel in single IV infusion up to 25 mg/m2. Limited pharmacokinetic data were available in patients with end-stage renal disease (n=2, CLCR < 15 mL/min/1.73m^2). *Hepatic Impairment* Cabazitaxel is extensively metabolized in the liver. A dedicated study in 43 cancer patients with hepatic impairment showed no influence of mild (total bilirubin >1 to ≤ 1.5 x ULN or AST >1.5 x ULN) or moderate (total bilirubin >1.5 to ≤3.0 x ULN) hepatic impairment on cabazitaxel pharmacokinetics. The maximum tolerated cabazitaxel dose (MTD) was 20 and 15 mg/m^2, respectively. In 3 patients with severe hepatic impairment (total bilirubin > 3 x ULN), a 39% decrease in clearance was observed when compared to patients with mild hepatic impairment (ratio=0.61, 90% CI: 0.36-1.05), indicating some effect of severe hepatic impairment on cabazitaxel pharmacokinetics. The MTD of cabazitaxel in patients with severe hepatic impairment was not established. Based on safety and tolerability data, cabazitaxel dose should be reduced in patients with mild hepatic impairment (see *Warnings and Precautions (5.6) and Use inSpecific Populations (8.7)]*). Cabazitaxel is contraindicated in patients with severe hepatic impairment *[see Contraindications* (4) *and Use in Specific Populations (8.7)]*. Drug interactions A drug interaction study of JEVTANA in 23 patients with advanced cancers has shown that repeated administration of ketoconazole (400 mg once daily), a strong CYP3A inhibitor, increased the exposure to cabazitaxel (5 mg/ m2 intravenous) by 25%. A drug interaction study of JEVTANA in 13 patients with advanced cancers has shown that repeated administration of aprepitant (125 or 80 mg once daily), a moderate CYP3A inhibitor, did not modify the exposure to cabazitaxel (15 mg/m2 intravenous). A drug interaction study of JEVTANA in 21 patients with advanced cancers has shown that repeated administration of rifampin (600 mg once daily), a strong CYP3A inducer, decreased the exposure to cabazitaxel (15 mg/m2 intravenous) by 17%. A drug interaction study of JEVTANA in 11 patients with advanced cancers has shown that cabazitaxel (25 mg/m2 administered as a single 1-hour infusion) did not modify the exposure to midazolam, a probe substrate of CYP3A.		11. CLINICAL PHARMACOLOGY

Prednisone or prednisolone administered at 10 mg daily did not affect the pharmacokinetics of cabazitaxel. Based on *in vitro* studies, the potential for cabazitaxel to inhibit drugs that are substrates of other CYP isoenzymes (1A2,-2B6,-2C9, -2C8, -2C19, -2E1, -2D6, and CYP3A4/5) is low. In addition, cabazitaxel did not induce CYP isozymes (-1A, -2C9 and -3A) *in vitro*.		