הודעה על החמרה (מידע בטיחות)

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אושר – 10.16

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שם תכשיר באנגלית: TYVASO Solution for Inhalation

מספר רישום: 144 71 33077

שם בעל הרישום: מעבדות רפא בע"מ

השינויים בעלון: צהוב=הוספה, ~~ירוק~~=מחיקה,

בעלון לרופא

פרק בעלון	טקסט חדש
5. Warnings and Precautions	… **5.4 Risk of Bleeding** Tyvaso inhibits platelet aggregation ~~there may be an increased~~ and increases the risk of bleeding. ~~particularly among patients receiving anticoagulant therapy.~~ …
6. Adverse Reactions	… **6.1 Adverse Reactions Identified in Clinical Trials** … Note: dizziness and diarrhea occurred in ≥ 10% of PAH patients receiving Tyvaso, but the difference between patients receiving Tyvaso to patients receiving placebo was <3% . *מדפי המבוא של העלון האמריקאי* The safety of Tyvaso was also studied in a long-term, open-label extension study in which 206 patients were dosed for a mean duration of 2.3 years, with a maximum exposure of 5.4 years. Eighty-nine (89%) percent of patients achieved the target dose of nine breaths, four times daily. Forty-two (42%) percent achieved a dose of 12 breaths four times daily. The adverse events during this chronic dosing study were qualitatively similar to those observed in the 12-week placebo controlled trial. In a prospective, observational study comparing patients taking Tyvaso (958 patient-years of exposure) and a control group (treatment with other approved therapies for PAH; 1094 patient-years), Tyvaso was associated with a higher rate of cough (16.2 per 100 patient-years vs. 10.9 per 100 pt-years), throat irritation (4.5 per 100 pt-years vs. 1.2 per 100 pt-years), nasal discomfort (2.6 per 100 pt-years vs. 1.3 per 100 pt-years), and hemoptysis (2.5 per 100 pt-years vs. 1.3 per 100 pt-years) compared to the control group. ,,,

8.1 Pregnancy Pregnancy Category B There are no adequate and well controlled studies with Tyvaso in pregnant women. Animal reproduction studies have not been conducted with treprostinil administered by the inhalation route. However, studies in pregnant rabbits using continuous subcutaneous (sc) infusions of treprostinil sodium at infusion rates higher than the recommended human sc infusion rate resulted in an increased incidence of fetal skeletal variations associated with maternal toxicity. Also, a study in pregnant rabbits administered oral treprostinil diolamine at exposures higher than those in humans resulted in external fetal and soft tissue malformations and fetal skeletal malformations *[see Nonclinical Toxicology (13.3)]*. Animal reproduction studies are not always predictive of human response.	**8. Use in specific populations**
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility A two-year rat carcinogenicity study was performed with treprostinil inhalation at target doses of 5.26, 10.6, and 34.1 mcg/kg/day. There was no evidence for carcinogenic potential associated with treprostinil inhalation in rats at systemic exposure levels up to 35 times the clinical exposure at the target maintenance dose of 54 mcg. In vitro and in vivo genetic toxicology studies did not demonstrate any mutagenic or clastogenic effects of treprostinil. Treprostinil sodium did not affect fertility or mating performance of male or female rats given continuous subcutaneous (sc) infusions at rates of up to 450 ng treprostinil/kg/min [about 59 times the recommended starting human sc infusion rate (1.25 ng/kg/min) and 8 times the average rate (9.3 ng/kg/min) achieved in clinical trials, on a ng/m^2 basis]. In this study, males were dosed from 10 weeks prior to mating and through the 2-week mating period. Females were dosed from 2 weeks prior to mating until gestational day 6. Oral administration of treprostinil diolamine to Tg.rasH2 mice at 0, 5, 10 and 20 mg/kg/day in males and 0, 3, 7.5 and 15 mg/kg/day in females daily for 26 weeks did not significantly increase the incidence of tumors. The exposures, when based on AUC, obtained at the highest dose levels used in males and females are about 208- and 460-fold, respectively, the human exposure following a single inhaled dose of 54 mcg. Treprostinil diolamine was tested *in vivo* in a rat micronucleus assay and did not induce an increased incidence of micronucleated polychromatic erythrocytes. **13.3 Developmental Toxicity** In pregnant rats, continuous sc infusions of treprostinil sodium during organogenesis and late gestational development, at rates as high as 900 ng treprostinil/kg/min (about 117 times the recommended starting human sc infusion rate and about 16 times the average rate achieved in clinical trials, on a ng/m^2 basis), resulted in no evidence of harm to the fetus. In pregnant rabbits, effects of continuous sc infusions of treprostinil during organogenesis were limited to an increased incidence of fetal skeletal variations (bilateral full rib or right rudimentary rib on lumbar vertebra 1) associated with maternal toxicity (reduction in body weight and food consumption) at an infusion rate of 150 ng treprostinil/kg/min (about 41 times the starting human sc infusion rate and 5 times the average rate achieved in clinical trials, on a ng/m^2 basis).	**13. Nonclinical toxicology**

In studies with treprostinil diolamine, no adverse effect doses for fetal viability / growth, fetal development (teratogenicity), and postnatal development were determined in rats. In pregnant rats, no evidence of harm to the fetus was observed following oral administration of treprostinil diolamine at the highest dose tested (20 mg/kg/day), which represents about 154 and 1479 times the human exposure, when based on C_{max} and AUC following a single dose of 54 mcg, respectively. In pregnant rabbits, external fetal and soft tissue malformations and fetal skeletal malformation occurred. The dose at which no adverse effects were seen (0.5 mg/kg/day) represents about 9 and 145 times the human exposure, when based on C_{max} and AUC following a single dose of 54 mcg, respectively. …	

בעלון לצרכן

פרק בעלון	טקסט חדש
4. תופעות לוואי	**…** *תופעות לוואי שכיחות פחות (מופיעות בפחות מ-4% מהמטופלים):* כאבים בלסת, בעצמות או בשרירים; אי נוחות באף, ליחה דמית. *תופעות לוואי נוספות הקשורות לדרך המתן של התרופה:* גירויים שונים במערכת הנשימה, דמם מהאף, ~~דריקת דם~~, צפצופים בנשימה, דלקת ריאות. **…**