ג'יי סי הלת' קר בע"מ

קיבוץ שפיים 60990 ישראל-
טל' 09-959-1111
פקס 09-958-3636

ינואר 2019

רופא/ה נכבד/ה
רוקח/ת נכבד/ה

הנדון: עדכון בעלונים לרופא ולצרכן של התכשיר Risperdal consta

ברצוננו להביא לידיעתכם כי חל עדכון בעלונים לרופא ולצרכן של התכשירים Risperdal consta על כל מינוניו.

- ההתוויות הרשומות בארץ:

Risperdal consta is indicated for the treatment of schizophrenia and schizoaffective disorders.
Risperdal consta is indicated as monotherapy for the maintenance treatment of bipolar I disorder to delay occurrence of mood episodes.
Risperdal consta is indicated for adjunctive maintenance treatment to delay occurrence of mood episodes in patients with frequently relapsing bipolar disorder

- בעלון לרופא חל תיקון בסעיפים:

5 WARNINGS AND PRECAUTIONS

5.1 Falls

Somnolence, postural hypotension, motor and sensory instability have been reported with the use of antipsychotics, including RISPERDAL CONSTA®, which may lead to falls and, consequently, fractures or other fall-related injuries. For patients, particularly the elderly, with diseases, conditions, or medications that could exacerbate these effects, assess the risk of falls when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

6 ADVERSE REACTIONS

- Falls [see Warnings and Precautions (5.8)]

8 USE IN SPECIFIC POPULATIONS

a. **Pregnancy**

Pregnancy ~~Category C.~~
Risk Summary
Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery *(see Clinical Considerations)*. Overall, available data from published epidemiologic studies of pregnant women exposed to risperidone have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes *(see Data)*. There are risks to the mother associated with untreated schizophrenia or bipolar I disorder and with exposure to antipsychotics, including RISPERDAL CONSTA®, during pregnancy *(see Clinical Considerations)*. Risperidone has been detected in plasma in adult subjects up to 8 weeks after a single-dose administration of RISPERDAL CONSTA® *[see Clinical Pharmacology (12.3)]*. The clinical significance of RISPERDAL CONSTA® administered before pregnancy or anytime during pregnancy is not known.

Oral administration of risperidone to pregnant mice caused cleft palate at doses 3 to 4 times the maximum recommended human dose (MRHD) with maternal toxicity observed at 4-times the

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MRHD based on mg/m^2 body surface area. Risperidone was not teratogenic in rats or rabbits at doses up to 6-times the MRHD based on mg/m^2 body surface area. Increased stillbirths and decreased birth weight occurred after oral risperidone administration to pregnant rats at 1.5-times the MRHD based on mg/m^2 body surface area. Learning was impaired in offspring of rats when the dams were dosed at 0.6-times the MRHD and offspring mortality increased at doses 0.1 to 3 times the MRHD based on mg/m^2 body surface area.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

There is a risk to the mother from untreated schizophrenia or bipolar I disorder, including increased risk of relapse, hospitalization, and suicide. Schizophrenia and bipolar I disorder are associated with increased adverse perinatal outcomes, including preterm birth. It is not known if this is a direct result of the illness or other comorbid factors.

Fetal/Neonatal Adverse Reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs, including RISPERDAL CONSTA®, during the third trimester of pregnancy. These symptoms have varied in severity. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization.

Data

Human Data

Published data from observational studies, birth registries, and case reports on the use of atypical antipsychotics during pregnancy do not report a clear association with antipsychotics and major birth defects. A prospective observational study including 6 women treated with risperidone demonstrated placental passage of risperidone. A retrospective cohort study from a Medicaid database of 9258 women exposed to antipsychotics during pregnancy did not indicate an overall increased risk for major birth defects. There was a small increase in the risk major of birth defects (RR=1.26, 95% CI 1.02-1.56) and of cardiac malformations (RR=1.26, 95% CI 0.88-1.81) in a subgroup of 1566 women exposed to risperidone during the first trimester of pregnancy; however, there is no mechanism of action to explain the difference in malformation rates.

Animal Data

Oral administration of risperidone to pregnant mice during organogenesis caused cleft palate at 10 mg/kg/day which is 3 times the MRHD of 16 mg/day based on mg/m^2 body surface area; maternal toxicity occurred at 4 times the MRHD. Risperidone was not teratogenic when administered orally to rats at 0.6 to 10 mg/kg/day and rabbits at 0.3 to 5 mg/kg/day, which are up to 6 times the MRHD of 16 mg/day risperidone based on mg/m^2 body surface area. Learning was impaired in offspring of rats dosed orally throughout pregnancy at 1 mg/kg/day which is 0.6 times the MRHD and neuronal cell death increased in fetal brains of offspring of rats dosed during pregnancy at 1 and 2 mg/kg/day which are 0.6 and 1.2 times the MRHD based on mg/m^2 body surface area; postnatal development and growth of the offspring were also delayed.

Rat offspring mortality increased during the first 4 days of lactation when pregnant rats were dosed throughout gestation at 0.16 to 5 mg/kg/day which are 0.1 to 3 times the MRHD of 16 mg/day based on mg/m^2 body surface area. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams:

~~The teratogenic potential of oral risperidone was studied in three embryofetal development studies in Sprague–Dawley and Wistar rats (0.63-10 mg/kg or 0.4 to 6 times the oral maximum recommended human dose [MRHD] on a mg/m^2 basis) and in one embryofetal development study in New Zealand rabbits (0.31-5 mg/kg or 0.4 to 6 times the oral MRHD on a mg/m^2 basis). The incidence of malformations was not increased compared to control in offspring of rats or rabbits given 0.4 to 6 times the oral MRHD on a mg/m^2 basis. In three reproductive studies in rats (two peri/post natal development studies and a multigenerational study), there was an increase in pup deaths during the first 4 days of lactation at doses of 0.16-5~~

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~~mg/kg or 0.1 to 3 times the oral MRHD on a mg/m^2 basis. It is not known whether these deaths were due to a direct effect on the fetuses or pups or to effects on the dams.~~

~~There was~~A ~~no~~ no-effect dose ~~for increased~~ could not be determined. The rate of stillbirths was increased at 2.5 mg/kg or 1.5 times the MRHD based on mg/m^2 body surface area.

In a~~rat pup mortality. In one peri/post-natal development study, there was an increase in stillborn rat pups at a dose of 2.5 mg/kg or 1.5 times the oral MRHD on a mg/m^2 basis. In a~~ rat cross- fostering study ~~in Wistar rats, toxic effects on the fetus or pups, as evidenced by a decrease in~~ the number of live ~~pups and an increase in~~offspring was decreased, ~~the number of dead pups at birth (Day 0),~~ stillbirths increased and ~~a decrease in~~the birth weight was decreased in ~~pups~~ offspring of drug- treated ~~dams were observed~~pregnant rats. In addition, ~~there was an increase inin~~ the number of deaths increased by Day 1 among ~~pups~~ offspring of drug-treated ~~dams~~pregnant rats, regardless of whether or not the ~~pups~~ offspring were cross-fostered. Risperidone also appeared to impair maternal behavior in that ~~pup~~ offspring body weight gain and survival (from Day~~s~~ 1 to 4 of lactation) were reduced in ~~pups~~ offspring born to control but reared by drug-treated dams. All of ~~t~~These effects ~~were all noted~~occurred at ~~the one dose of risperidone tested, i.e.,~~ 5 mg/kg ~~or~~ which is 3 times the ~~oral~~ MRHD based on ~~a~~ mg/m^2 ~~basis~~and the only dose tested in the study.

~~No studies were conducted with RISPERDAL® CONSTA®.~~
~~Placental transfer of risperidone occurs in rat pups. There are no adequate and well controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone *in utero*. The causal relationship to oral RISPERDAL® therapy is unknown.~~

~~Non_Teratogenic Effects~~

~~Neonates exposed to antipsychotic drugs (including RISPERDAL®) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.~~

~~RISPERDAL® CONSTA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.~~

~~Labor and Delivery~~

~~The effect of RISPERDAL® CONSTA® on labor and delivery in humans is unknown.~~

~~Nursing Mothers~~

~~Risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Therefore, women should not breast-feed during treatment with RISPERDAL® CONSTA® and for at least 12 weeks after the last injection.~~

b. Lactation

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Risk Summary

Limited data from published literature reports the presence of risperidone and its metabolite, 9-hydroxyrisperidone, in human breast milk at relative infant dose ranging between 2.3% and 4.7% of the maternal weight-adjusted dosage. There are reports of sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements) in breastfed infants exposed to risperidone *(see Clinical Considerations)*. Risperidone has been detected in plasma in adult subjects up to 8 weeks after a single-dose administration of RISPERDAL CONSTA® *[see Clinical Pharmacology (12.3)]*, and the clinical significance on the breastfed infant is not known. There is no information on the effects of risperidone on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RISPERDAL CONSTA® and any potential adverse effects on the breastfed child from RISPERDAL CONSTA® or from the mother's underlying condition.

Clinical Considerations

Infants exposed to RISPERDAL CONSTA® through breastmilk should be monitored for excess sedation, failure to thrive, jitteriness, and extrapyramidal symptoms (tremors and abnormal muscle movements).

c. Females and Males of Reproductive Potential

Infertility

Females

Based on the pharmacologic action of risperidone (D2 receptor antagonism), treatment with RISPERDAL CONSTA® may result in an increase in serum prolactin levels, which may lead to a reversible reduction in fertility in females of reproductive potential *[see Warnings and Precautions (5.6)]*.

- בעלון לצרכן חל תיקון בסעיפים הבאים:

אזהרה: עלייה בתמותה בחולים קשישים הסובלים מדמנציה הקשורה לפסיכוזות.
חולים קשישים החולים בדמנציה הקשורה לפסיכוזות המטופלים בתרופות אנטי-פסיכוטיות הם בעלי סיכון מוגבר למוות. ריספרדל קונסטה אינה מאושרת לחולים עם דמנציה הקשורה לפסיכוזות.

השינויים מסומנים בעלון המצורף כאשר הטקסט המודגש הוסף לעלון ואילו הטקסט המחוק מודגש עם קו חוצה.

העלון לרופא נשלח לפרסום במלואו למאגר התרופות שבאתר משרד הבריאות.

כמו כן, ניתן לקבלו מודפס בפניה אלינו לטלפון 09-9591111 .

בברכה,

צפריר כהן
רוקח ממונה