יולי 2018

רופא/ה, רוקח/ת נכבד/ה,

הנדון: Dexilant 30mg & 60mg
דקסילנט 30 מ"ג ו-60 מ"ג

אנו מבקשים להודיעך כי העלונים לרופא ולצרכן של התכשירים שבנדון עודכנו ביולי 2018.

ההתוויות להן רשום התכשיר:

Dexilant 30 is indicated in adults and in adolescents aged 12 to 17 years for the following:

- Maintenance of healed erosive reflux oesophagitis and maintenance of relief of heartburn.
- Short-term treatment of heartburn and acid regurgitation associated with symptomatic non-erosive gastro-oesophageal reflux disease (GORD).

Dexilant 60 is indicated in adults and in adolescents aged 12 to 17 years for the following:

- Treatment of erosive reflux oesophagitis

צורת מינון: Modified release capsules

מרכיב פעיל: Dexlansoprazole 30 mg / Dexlansoprazole 60 mg

בעמודים הבאים מפורטים הסעיפים בהם נעשו שינויים אשר מהווים החמרה או שינויים משמעותיים שחלו בעלונים.
למידע נוסף, יש לעיין בעלונים לצרכן ולרופא כפי שאושרו על ידי משרד הבריאות.

העלונים המעודכנים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות:
http://www.old.health.gov.il/units/pharmacy/trufot/index.asp
כמו כן, ניתן לקבלם מודפסים על ידי פניה לחברת טקדה ישראל בע"מ, רח' אפעל 25, פתח תקוה, 03-3733140.

בברכה,

חן פרידליס
רוקחת ממונה
טקדה ישראל בע"מ

להלן פירוט השינויים העיקריים בעלון לרופא (טקסט שנוסף מסומן באדום עם קו תחתון, טקסט שהושמט מסומן כטקסט כחול עם קו חוצה):

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6 WARNINGS AND PRECAUTIONS

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6.10 Fundic Gland Polyps

PPI use is associated with an increased risk of fundic gland polyps that increases with long-term use, especially beyond one year. Most PPI users who developed fundic gland polyps were asymptomatic and fundic gland polyps were identified incidentally on endoscopy. Use the shortest duration of PPI therapy appropriate to the condition being treated.

7 ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in labeling:

- Acute Interstitial Nephritis *[see Warnings and Precautions (6.2)]*
- Clostridium difficile Associated Diarrhea *[see Warnings and Precautions (6.3)]*
- Bone Fracture *[see Warnings and Precautions (6.4)]*
- Cutaneous and Systemic Lupus Erythematosus [see *Warnings and Precautions (6.5)*]
- Cyanocobalamin (Vitamin B-12) Deficiency [see *Warnings and Precautions (6.6)*]
- Hypomagnesemia *[see Warnings and Precautions (6.7)]*
- Fundic Gland Polyps *[see Warnings and Precautions (6.10)]*

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7.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval of DEXILANT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura

Ear and Labyrinth Disorders: deafness

Eye Disorders: blurred vision

Gastrointestinal Disorders: oral edema, pancreatitis, fundic gland polyps

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9 USE IN SPECIFIC POPULATIONS

9.1 Pregnancy

Risk Summary

There are no studies with dexlansoprazole use in pregnant women to inform a drug-associated risk.

Dexlansoprazole is the R-enantiomer of lansoprazole, and published observational studies of lansoprazole use during pregnancy did not demonstrate an association of adverse pregnancy-related outcomes with lansoprazole *(see Data)*.

In animal reproduction studies, ~~no effects on embryo-fetal development were observed with the~~ oral administration of ~~oral dexlansoprazole to rabbits~~ lansoprazole to rats during organogenesis ~~at doses up to nine~~ through lactation at 1.8 times the maximum recommended human ~~dose (MRHD) (based on body surface area) or with administration of oral lansoprazole to rats and rabbits during organogenesis at doses up to 40 and 16 times the MRHD (based on body surface area), respectively *[see Data]*.~~dexlansoprazole dose produced reductions in the offspring in femur weight, femur length, crown-rump length and growth plate thickness (males only) on postnatal Day 21 *(see Data)*. These effects were associated with reduction in body weight gain. Advise pregnant women of the potential risk to a fetus.

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~~-~~to 4% and 15~~-~~ to 20%, respectively.

Data

Human Data

Dexlansoprazole is the R-enantiomer of lansoprazole. Available data from published observational studies failed to demonstrate an association of adverse pregnancy-related outcomes and lansoprazole use. Methodological limitations of these observational studies cannot definitely establish or exclude any drug-associated risk during pregnancy. In a prospective study by the European Network of Teratology Information Services, outcomes from a group of 62 pregnant women administered median daily doses of 30 mg of lansoprazole were compared to a control group of 868 pregnant women who did not take any PPIs. There was no difference in the rate of major malformations between women exposed to PPIs and the control group, corresponding to a Relative Risk (RR)=1.04, [95% Confidence Interval (CI) 0.25-4.21]. In a population-based retrospective cohort study covering all live births in Denmark from 1996 to 2008, there was no significant increase in major birth defects during analysis of first trimester exposure to lansoprazole in 794 live births. A meta-analysis that compared 1,530 pregnant women exposed to PPIs in at least the first trimester with 133,410 unexposed pregnant women showed no significant increases in risk for congenital malformations or spontaneous abortion with exposure to PPIs (for major malformations Odds Ratio (OR)=1.12, [95% CI 0.86-1.45] and for spontaneous abortions OR=1.29, [95% CI 0.84-1.97]).

Animal Data

An embryo-fetal development study conducted in rabbits at oral dexlansoprazole doses up to 30 mg/kg/day (approximately nine times the maximum recommended human dexlansoprazole dose [60 mg/day] based on body surface area) during organogenesis showed no effects on fetuses due to dexlansoprazole. In addition, embryo-fetal development studies performed in rats with oral lansoprazole at doses up to 150 mg/kg/day (40 times the recommended human lansoprazole dose based on body surface area) during organogenesis and in rabbits with oral lansoprazole at doses up to 30 mg/kg/day (16 times the recommended human lansoprazole dose based on body surface area) during organogenesis revealed no effects on fetuses due to

lansoprazole.

A pre- and postnatal developmental toxicity study in rats with additional endpoints to evaluate bone development was performed with lansoprazole at oral doses of 10 to 100 mg/kg/day (0.2 to 1.8 times the maximum recommended human dexlansoprazole dose of 60 mg based on dexlansoprazole AUC [area under the plasma concentration-time curve]) administered during organogenesis through lactation. Maternal effects observed at 100 mg/kg/day (1.8 times the maximum recommended human dexlansoprazole dose of 60 mg based on dexlansoprazole AUC) included increased gestation period, decreased body weight gain during gestation, and decreased food consumption. The number of stillbirths was increased at this dose, which may have been secondary to maternal toxicity. Body weight of pups was reduced at 100 mg/kg/day starting on postnatal Day 11. Femur weight, femur length, and crown-rump length were reduced at 100 mg/kg/day on postnatal Day 21. Femur weight was still decreased in the 100 mg/kg/day group at age 17 to 18 weeks. Growth plate thickness was decreased in the 100 mg/kg/day males on postnatal Day 21, and was increased in the 30 and 100 mg/kg/day males at age 17 to 18 weeks. The effects on bone parameters were associated with reduction in body weight gain.

9.2 Lactation

Risk Summary

There is no information regarding the presence of dexlansoprazole in human milk, the effects on the breastfed infant, or the effects on milk production. However, lansoprazole and its metabolites are present in rat milk ~~*[see Data]*~~. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DEXILANT and any potential adverse effects on the breastfed child from DEXILANT or from the underlying maternal condition.

~~Data~~

~~When [^{14}C] lansoprazole was administered orally at 2 mg/kg to lactating rats 14 days after parturition, milk collected at 0.5, 2 and 6 hours after the lansoprazole dose contained 2 to 6 fold higher concentrations of radioactivity than plasma. Almost all of the radioactivity was determined to be from lansoprazole metabolites.~~

9.3 Pediatric Use

The use of DEXILANT is not recommended for the treatment of symptomatic non erosive GORD in pediatric patients one month to less than one year of age because lansoprazole (the racemic mixture) was not shown to be effective in a multicenter, double-blind controlled trial, and nonclinical studies with lansoprazole have demonstrated an adverse effect of heart valve thickening and bone changes.

The safety and effectiveness of DEXILANT have not been established in pediatric patients less than 12 years of age. DEXILANT is not recommended in pediatric patients less than 12 years of age. Nonclinical studies in juvenile rats with lansoprazole have demonstrated an adverse effect of heart valve thickening and bone changes at lansoprazole doses higher than the maximum recommended equivalent human dose, as described below in *Juvenile Animal Toxicity Data*.

The safety and effectiveness of DEXILANT have been established in pediatric patients 12 to 17 years of age for the healing of all grades of erosive reflux oesophagitis, the maintenance of healed erosive reflux oesophagitis and maintenance of relief of heartburn, and treatment of heartburn associated with symptomatic non-erosive GORD.

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The adverse reaction profile in patients 12 to 17 years of age was similar to adults.

~~The safety and effectiveness of DEXILANT have not been established in pediatric patients less than 12 years of age.~~

~~The use of DEXILANT is not recommended for symptomatic non-erosive GORD in pediatric patients less than one year of age because studies in this class of drugs have not demonstrated efficacy.~~

Juvenile Animal Toxicity Data
In a juvenile rat study, adverse effects on bone growth and development and heart valves were observed at lansoprazole doses higher than the maximum recommended equivalent human dose.

An eight-week oral toxicity study with a four-week recovery phase was conducted in juvenile rats with lansoprazole administered from postnatal Day 7 (age equivalent to neonatal humans) through 62 (age equivalent to approximately 14 years in humans) at doses of 40 to 500 mg/kg/day.

Heart valve thickening occurred at a lansoprazole dose of 500 mg/kg/day (approximately three to five times the expected dexlansoprazole exposure in pediatric patients less than 12 years of age based on AUC). Heart valve thickening was not observed at the next lower dose (250 mg/kg/day) and below. The findings trended towards reversibility after a four-week drug-free recovery period. The relevance of heart valve thickening in this study to pediatric patients less than 12 years of age is unknown. These findings are not relevant for patients 12 years of age and older. No effects on heart valves were observed in a 13-week intravenous toxicity study of lansoprazole in adolescent rats (approximately 12 years human age equivalence) at systemic exposures similar to those achieved in the eight-week oral toxicity study in juvenile (neonatal) rats.

In the eight-week oral toxicity study of lansoprazole, doses equal to or greater than 100 mg/kg/day produced delayed growth, with impairment of weight gain observed as early as postnatal Day 10 (age equivalent to neonatal humans). At the end of treatment, the signs of impaired growth at 100 mg/kg/day and higher included reductions in body weight (14% to 44% compared to controls), absolute weight of multiple organs, femur weight, femur length and crown-rump length. Femoral growth plate thickness was reduced only in males and only at the 500 mg/kg/day dose. The effects related to delayed growth persisted through the end of the 4-week recovery period. Longer term data were not collected.

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להלן פירוט השינויים העיקריים בעלון לצרכן (טקסט שנוסף מסומן באדום עם קו תחתון, טקסט שהושמט מסומן כטקסט כחול עם קו חוצה):

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2. לפני שימוש בתרופה

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לפני הטיפול בדקסילנט, ספר לרופא אם:

- נאמר לך שיש לך רמות מגנזיום נמוכות בדם.
- אתה סובל מבעיות בכבד.
- אתה סובל מבעיות רפואיות אחרות.
- אי-פעם סבלת מתגובה עורית לאחר טיפול בתרופה דומה לדקסילנט, המפחיתה את החומציות בקיבה.
- את בהריון או מתכננת להיכנס להריון. ~~לא ידוע אם שימוש ב~~דקסילנט עלול לפגוע בעובר. דברי עם רופאך לגבי סיכונים אפשריים לעובר במידה ואת נוטלת דקסילנט במהלך הריון.
- את מניקה או מתכננת להיניק. לא ידוע אם דקסילנט עובר בחלב-אם או אם משפיע על תינוקך או על חלב-האם.
  דברי עם רופאך לגבי הדרך הטובה ביותר באמצעותה תוכלי להזין את תינוקך, במידה ואת נוטלת דקסילנט.

אזהרות נוספות:
- אם אתה מפתח פריחה עורית, במיוחד באיזורים החשופים לשמש, יש ליידע את הרופא בהקדם האפשרי, מאחר וייתכן שתצטרך להפסיק את הטיפול בדקסילנט. זכור לציין גם כל תופעת לוואי אחרת שהופיעה במקביל, כגון כאב פרקים.
- **גידולי בטן (פוליפים בבלוטת הפונדוס - fundic gland polyps)** – מטופלים אשר נוטלים תרופות מסוג מעכבי משאבת פרוטון PPI למשך זמן רב בעלי סיכון מוגבר לפתח סוג מסויים של גידול בטן הנקרא פוליפים בבלוטת הפונדוס (fundic gland polyps), במיוחד לאחר נטילת תרופות PPI במשך יותר משנה אחת.

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הריון והנקה

אם הינך בהריון או מיניקה או סבורה שהינך בהריון או מתכננת להרות יש להיוועץ ברופא לפני השימוש בתרופה.
דקסילנט עלול לפגוע בעובר. דברי עם רופאך לגבי סיכונים אפשריים לעובר במידה ואת נוטלת דקסילנט במהלך הריון.

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4. תופעות לוואי

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דקסילנט עלול לגרום לתופעות לוואי חמורות הכוללות:

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- **גידולי בטן (פוליפים בבלוטת הפונדוס - fundic gland polyps)** – מטופלים אשר נוטלים תרופות מסוג מעכבי משאבת פרוטון PPI למשך זמן רב בעלי סיכון מוגבר לפתח סוג מסויים של גידול בטן הנקרא פוליפים בבלוטת הפונדוס (fundic gland polyps), במיוחד לאחר נטילת תרופות PPI במשך יותר משנה אחת.

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תופעות לוואי ששכיחותן לא ידועה (אין אפשרות להעריך את השכיחות על סמך הנתונים הקיימים):
- ירידה במספר תאי הדם האדומים. זה יכול לגרום לחיוורון, לחולשה, לקושי לבצע פעילות פיזית, לסחרחורת, לעייפות ולבלבול
- פצעים או דימומים כתוצאה מספירה נמוכה מן הרגיל של טסיות דם הנובעת מגורם לא ידוע
- תגובות חמורות בעור
- ראייה מטושטשת
- חירשות
- דלקת כבד (hepatitis) כתוצאה מנטילת תרופות (עם תסמינים כגון אובדן תיאבון, כאב ראש, בחילה, תשישות, חום, צהבת, צואה בהירה או בצבע גיר, שתן כהה)
- פריחה, ייתכן שתהיה מלווה בכאבי פרקים.
- **פוליפים בבלוטת הפונדוס (fundic gland polyps)**

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