נספח 2 - נוסח הפצה לפי נוהל 49:

תאריך: מרץ 2022

רופא /ה, רוקח/ת נכבד/ה

חברת טבע מודיעה על העדכונים הבאים בעלונים לצרכן ולרופא של התכשיר:

ZYLET Ophtalmic Suspension

זיילט תרחיף לעיניים

Contains: 5 mg/mL (0.5%) loteprednol etabonate and 3 mg/mL (0.3%) tobramycin

עדכונים בעלון לצרכן ובעלון לרופא

התוויה כפי שאושרה בתעודת הרישום:

ZYLET is indicated for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.
Ocular steroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, and where the inherent risk of steroid use in certain infective conjunctivitides is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation or thermal burns, or penetration of foreign bodies
The use of a combination drug with an anti-infective component is indicated where the risk of superficial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye
The particular anti-infective drug in this product (tobramycin) is active against the following common bacterial eye pathogens:
Staphylococci, including *S. aureus* and *S. epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains. Streptococci, including some of the Group A-beta-hemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniaePseudomonas aeruginosa, Escherichia coli,*

Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis, Morganella morganii, most *Proteus vulgaris* strains*, Haemophilus influenzae,* and *H. aegyptius, Moraxella lacunata, Acinetobacter calcoaceticus* and some *Neisseria* species.

ברצוננו להודיע שהעלון לצרכן עודכן, בפירוט שלהלן כלולים העדכונים העיקריים בלבד (תוספות מסומנות באדום והסרות מידע כטקסט מחוק):

מידע חשוב על חלק מהמרכיבים של התרופה
התרופה מכילה את החומר המשמר בנזלקוניום כלוריד 0.01%, העלול להיספג על ידי עדשות מגע רכות ולשנות את צבען. יש להסיר את עדשות המגע לפני השימוש בתרופה ולהחזירן לאחר 15 דקות מעת השימוש. בנזלקוניום כלוריד עלול גם לגרום לגירוי בעין, בייחוד אם אתה סובל מעיניים יבשות, או הפרעות בקרנית. אם יש לך תחושה לא תקינה בעיניים, עקצוץ או כאב בעין לאחר השימוש בתרופה, פנה לרופא שלך.

ברצוננו להודיע שהעלון לרופא עודכן, בפירוט שלהלן כלולים העדכונים העיקריים בלבד (תוספות מסומנות באדום והסרות מידע כטקסט מחוק):

5.8 Risk of Contamination
Do not allow the dropper tip to touch any surface, as this may contaminate the suspension.

5.9 Contact Lens Wear
As with all ophthalmic preparations containing benzalkonium chloride, patients should be advised not to wear soft contact lenses when using ZYLET.

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies with loteprednol etabonate or tobramycin in pregnant women**.**

Loteprednol etabonate produced teratogenicity at clinically relevant doses in the rabbit and rat when administered orally during pregnancy. Loteprednol etabonate produced malformations when administered orally to pregnant rabbits at doses ≥ 0.54 times the recommended human ophthalmic dose (RHOD) and to pregnant rats at doses ≥ 13 times the RHOD. In pregnant rats receiving oral doses of loteprednol etabonate during the period equivalent to the last trimester of pregnancy through lactation in humans, survival of offspring was reduced at doses ≥ 1.3 times the RHOD. Maternal toxicity was observed in rats at doses ≥ 135 times the RHOD, and a maternal no observed adverse effect level (NOAEL) was established at 13 times the RHOD.

Abortions were observed in pregnant rabbits administered tobramycin via subcutaneous injection at 180 times the RHOD. Tobramycin did not affect fetal development when administered by subcutaneous injection to pregnant rats at doses 450 times the RHOD.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data

Animal Data

Embryofetal studies were conducted in pregnant rabbits administered loteprednol etabonate by oral gavage on gestation days 6 to 18, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations at doses ≥ 0.1 mg/kg/day (0.54 times the recommended human ophthalmic dose (RHOD) based on body surface area, assuming 100% absorption of loteprednol etabonate). Spina bifida (including meningocele) was observed at doses ≥ 0.1 mg/kg/day, and exencephaly and craniofacial malformations were observed at doses ≥ 0.4 mg/kg/day (2.1 times the RHOD). At 3 mg/kg/day (16 times the RHOD), loteprednol etabonate was associated with increased incidences of abnormal left common carotid artery, limb flexures, umbilical hernia, scoliosis, and delayed ossification. Abortion and embryofetal lethality (resorption) occurred at doses ≥ 6 mg/kg/day (32 times the RHOD). A NOAEL for developmental toxicity was not established in this study. The NOAEL for maternal toxicity in rabbits was 3 mg/kg/day.

Embryofetal studies were conducted in pregnant rats administered loteprednol etabonate by oral gavage on gestation days 6 to 15, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations, including absent innominate artery at doses ≥ 5 mg/kg/day (13 times the RHOD); and cleft palate, agnathia, cardiovascular defects, umbilical hernia, decreased fetal body weight and decreased skeletal ossification at doses ≥ 50 mg/kg/day (135 times the RHOD). Embryofetal lethality (resorption) was observed at 100 mg/kg/day (270 times the RHOD). The NOAEL for developmental toxicity in rats was 0.5 mg/kg/day (1.3 times the RHOD). Loteprednol etabonate was maternally toxic (reduced body weight gain) at doses of ≥ 50 mg/kg/day. The NOAEL for maternal toxicity was 5 mg/kg/day.

A peri-/postnatal study was conducted in rats administered loteprednol etabonate by oral gavage from gestation day 15 (start of fetal period) to postnatal day 21 (the end of lactation period). At doses ≥ 0.5 mg/kg/day (1.3 times the RHOD), reduced survival was observed in live-born offspring. Doses ≥ 5 mg/kg/day (13 times the RHOD) caused umbilical hernia/incomplete gastrointestinal tract. Doses ≥ 50 mg/kg/day (135 times the RHOD) produced maternal toxicity (reduced body weight gain, death), decreased number of live-born offspring, decreased birth weight, and delays in postnatal development. A developmental NOAEL was not established in this study. The NOAEL for maternal toxicity was 5 mg/kg/day.

An embryofetal study was conducted in pregnant rabbits administered 20 or 40 mg/kg/day tobramycin by subcutaneous injection on gestational days 6 to 18, to target the period of organogenesis. Abortions and maternal toxicity (renal nephrosis and cortical tubular necrosis) were observed at both dose levels. The developmental and maternal lowest observed adverse effect level (LOAEL) is 20 mg/kg/day (180 times the RHOD based on body surface area, assuming 100% absorption of tobramycin). An embryofetal study was conducted in pregnant rats administered 50 or 100 mg/kg/day tobramycin by subcutaneous injection on gestational days 6 to 15, to target the period of organogenesis. No effects on development, reproduction, or maternal toxicity were reported. The developmental and maternal NOAEL is 100 mg/kg/day (450 times the RHOD).

8.2 Lactation

There are no data on the presence of loteprednol etabonate or tobramycin in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for ZYLET and any potential adverse effects on the breastfed infant from ZYLET.

18 PATIENT COUNSELING INFORMATION

Risk of Contamination

This product is sterile when packaged. Advise patients not to allow the dropper tip to touch any surface, as this may contaminate the suspension.

Risk of Secondary Infection

Advise patients to consult a physician if pain develops, redness, itching or inflammation becomes aggravated.

Contact Lens Wear

As with all ophthalmic preparations containing benzalkonium chloride, advise patients not to wear soft contact lenses when using ZYLET.