דצמבר 2025

רופא/ה נכבד/ה,
רוקח/ת נכבד/ה,

הנדון: ALPHAGAN P

Dosage Form: Eye drops, solution
Composition: BRIMONIDINE TARTRATE 0.15%w\v

שלום רב,

חברת AbbVie Biopharmaceuticals Ltd. מבקשת להודיע, כי העלון לרופא והעלון לצרכן של התכשיר שבנדון עודכנו. בהודעה זו מצוינים סעיפים בהם נעשה **שינוי מהותי** או **שינוי המהווה החמרה**. מידע שהתווסף מצוין באדום עם קו תחתי. מידע שנמחק מצוין ~~בכחול עם קו חוצה~~. עדכונים נוספים אשר אינם מהווים החמרה או שאינם מהותיים, אינם נכללים בהודעה זו.

ההתוויה המאושרת על ידי משרד הבריאות:

Alphagan P is indicated for lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

שינויים מהותיים בעלון לרופא:

7 WARNINGS AND PRECAUTIONS

[...]

7.3 Contamination of Topical Ophthalmic Products After Use

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface. Do not touch the tip of the dispensing container to the eye or surrounding structures. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

[...]

8 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Potentiation of Vascular Insufficiency *[see Warnings and Precautions (7.1)]*
- Severe Cardiovascular Disease *[see Warnings and Precautions (7.2)]*
- Contamination of Topical Ophthalmic Products after Use *[see Warnings and Precautions (7.3)]*
- Neonates and Infants (Pediatric Patients Younger than 2 Years Old) *[see Contraindications (6.1)]*

[...]

10 USE IN SPECIFIC POPULATIONS

10.1 Pregnancy

~~Pregnancy Category B: Teratogenicity studies have been performed in animals.~~

~~Brimonidine tartrate was not teratogenic when given orally during gestation days 6 through 15 in rats and days 6 through 18 in rabbits. The highest doses of brimonidine tartrate in rats (2.5 mg/kg/day) and rabbits (5.0 mg/kg/day) achieved AUC exposure values 360- and 20-fold higher, or 260- and 15-fold higher, respectively, than similar values estimated in humans treated with **ALPHAGAN® P** , 1 drop in both eyes three times daily.~~

Risk Summary

[...]

Data

Human Data

Limited available data from postmarketing safety reports and published literature with topical use of brimonidine ophthalmic solution in pregnant women are insufficient to inform a drug-associated risk of pregnancy-related adverse outcomes including miscarriage, stillbirth, congenital anomaly, and events experienced by offspring while breastfeeding.

Animal Data

Embryofetal studies were conducted in pregnant rabbits administered brimonidine tartrate by daily oral gavage on gestation days 6 to 18, to target the period of organogenesis. Brimonidine caused miscarriage at 5 mg/kg/day (approximately 50-times the recommended human ophthalmic dose [RHOD] based on AUC, for brimonidine tartrate 0.15%). The no observed adverse effect level (NOAEL) for developmental toxicity in rabbits was 1 mg/kg/day (approximately 6-fold the RHOD based on AUC, for brimonidine tartrate 0.15%). No treatment-related malformations were observed in rabbits. Signs of maternal sedation and fatigue were observed at all dose levels; the lowest observed adverse effect level (LOAEL) for maternal toxicity was 5 mg/kg/day, based on the dose response for these signs.

Embryofetal studies were conducted in pregnant rats administered brimonidine tartrate by daily oral gavage on gestation days 6 to 15, to target the period of organogenesis. The NOAEL for developmental toxicity was 2.5 mg/kg/day (approximately 750-fold the RHOD based on AUC, for brimonidine tartrate 0.15%). No treatment-related malformations were observed in rats. The LOAEL for maternal toxicity was 2.5 mg/kg/day, based on signs of sedation and fatigue. The maternal NOAEL was 1.0 mg/kg/day (180-fold the RHOD based on AUC, for brimonidine tartrate 0.15%).

After pregnant rats received a single oral dose of ^{14}C-brimonidine tartrate, brimonidine and metabolites crossed the placenta and were detectable in fetal blood and organs.

10.2 Lactation

Risk Summary

~~**10.2 Nursing Mothers**~~

It is not known whether brimonidine tartrate is excreted in human milk~~, although in~~. In animal studies, brimonidine tartrate has been shown to ~~be~~ cross the blood-brain barrier and is excreted into breast milk~~.~~ after oral administration to lactating rats *(see Data)*. Because of the potential for serious adverse reactions, including central nervous system depression and apnea, ~~from~~ from **ALPHAGAN® P** in nursing infants,

~~a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother~~ ALPHAGAN P is not recommended for use during lactation.

Data

Animal Data

After a single oral dose of ^{14}C-labeled brimonidine tartrate to lactating rats, brimonidine and metabolites were detected in milk. After male and female rats received a single oral dose of ^{14}C-brimonidine tartrate, brimonidine crossed the blood-brain barrier. Radiolabel was detected in the cerebellum, cerebrum, and spinal cord.

[...]

13.2 Pharmacokinetics

[...]

Distribution

~~The protein binding of brimonidine has not been studied.~~

Brimonidine was approximately 29% bound to plasma proteins in healthy subjects.

[...]

14 NONCLINICAL TOXICOLOGY

14.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

No compound-related carcinogenic effects were observed in either mice or rats following a 21-month and 24-month study, respectively. In these studies, dietary administration of brimonidine tartrate at doses up to 2.5 mg/kg/day in mice and 1 mg/kg/day in rats achieved approximately ~~150 and 120 times or 90~~ 93 and ~~80~~ 76 times~~, respectively, the plasma C_{max} drug concentration in humans treated with one drop of **ALPHAGAN® P** 0.15% into both eyes 3 times per day,~~ the recommended ~~daily~~ human ophthalmic dose~~.~~ (RHOD) based on C_{max} respectively for brimonidine tartrate 0.15%.

Mutagenesis

Brimonidine tartrate was not mutagenic or clastogenic in a series of *in vitro* and *in vivo* studies including the Ames bacterial reversion test, chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells, and three *in vivo* studies in CD-1 mice: a host-mediated assay, cytogenetic study, and dominant lethal assay.

~~Reproduction~~ Impairment of Fertility

A reproduction and fertility ~~studies~~ study in rats with brimonidine tartrate demonstrated no adverse effect on male or female fertility at oral doses ~~which achieve~~ up to 1 mg/kg (approximately ~~125 and 90~~180~~ ~~ times the ~~systemic exposure following the maximum~~ recommended human ophthalmic dose ~~of **ALPHAGAN® P** 0.1% or 0.15%,~~ [RHOD] based on estimated AUC)~~respectively.~~ for brimonidine tartrate 0.15%.

<u>שינויים מהותיים בעלון לצרכן:</u>

2. לפני השימוש בתרופה

[...]

אזהרות מיוחדות הנוגעות לשימוש בתרופה

לפני הטיפול באלפאגן P, ספר לרופא אם:

[...]

- אם אתה סובל או סבלת בעבר ממחלה כלשהיא על פני העין שלך. כאשר אתה משתמש בבקבוק רב מינון, כמו זה, אתה עלול לזהם אותו בשוגג ומצב זה יכול לגרום לזיהום על פני העין שלך. <u>אין לתת לקצה הבקבוק לגעת בעין או באזור אחר. שימוש בטיפות עיניים מזוהמות עלול לגרום לאובדן ראיה כתוצאה מנזק חמור לעין.</u>

[...]

הריון והנקה

אם את בהיריון או מיניקה, חושבת שאת בהיריון או מתכננת להרות, עלייך להיוועץ ברופא או ברוקח לפני נטילת תרופה זו.

<u>אלפאגן P אינו מומלץ לשימוש בהנקה.</u>

העלון לרופא ולצרכן נשלחו למאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום, AbbVie Biopharmaceuticals Ltd., רחוב החרש 4, הוד-השרון או בטלפון 09–7909600.

בברכה,
חברת אבווי ביופארמה בע"מ