NOVARTIS

מרץ 2022

רופא/ה נכבד/ה, רוקח/ת נכבד/ה,

הנדון: Lucentis, solution for injection, 10 mg/ml
לוסנטיס

התוויה חדשה

אנו שמחים להודיעכם על רישום התוויה חדשה לתכשיר:
The treatment of proliferative diabetic retinopathy (PDR)

התכשיר רשום בישראל גם להתוויות הבאות:

Treatment of patients with neovascular (wet) age-related macular degeneration (AMD).

Treatment of adult patients with visual impairment due to diabetic macular oedema (DME).

The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (RVO).

The treatment of visual impairment due to choroidal neovascularization (CNV).

Lucentis is indicated in preterm infants for:
The treatment of retinopathy of prematurity (ROP) with zone I (stage 1+, 2+, 3 or 3+), zone II (stage 3+) or AP-ROP (aggressive posterior ROP) disease.

המרכיב הפעיל: Ranibizumab 10 mg /mL

העלונים לרופא ולצרכן עודכנו עם ההתוויה החדשה ועם עדכונים שונים נוספים. השינויים המהותיים מפורטים בהמשך המכתב.

למידע נוסף יש לעיין בעלון לרופא העדכני כפי שאושר ע"י משרד הבריאות הישראלי.

העלון לרופא והעלונים לצרכן נשלחו למאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על-ידי פניה לבעל הרישום.

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להלן השינויים המהותיים בעלונים לרופא ולצרכן:

בעלון לרופא:

4.1 Therapeutic indications

- The treatment of proliferative diabetic retinopathy (PDR)

4.2 Posology and method of administration

Posology
Adults
The recommended dose for Lucentis in adults is 0.5 mg given as a single intravitreal injection. This corresponds to an injection volume of 0.05 ml. The interval between two doses injected into the same eye should be at least four weeks.

Treatment in adults is initiated with one injection per month until maximum visual acuity is achieved and/or there are no signs of disease activity. i.e. no change in visual acuity and in other signs and symptoms of the disease under continued treatment. In patients with wet AMD, DME, PDR and RVO, initially, three or more consecutive, monthly injections may be needed.

Thereafter, monitoring and treatment intervals should be determined by the physician and should be based on disease activity, as assessed by visual acuity and/or anatomical parameters.

If, in the physician's opinion, visual and anatomic parameters indicate that the patient is not benefiting from continued treatment, Lucentis should be discontinued.

Monitoring for disease activity may include clinical examination, functional testing or imaging techniques (e.g. optical coherence tomography or fluorescein angiography).

If patients are being treated according to a treat-and-extend regimen, ~~for example~~once maximum visual acuity is achieved and/or there are no signs of disease activity, the treatment intervals can be extended stepwise until signs of disease activity or visual impairment recur. The treatment interval should be extended by two weeks at a time for wet AMD and may be extended by up to one month at a time for DME. For PDR and RVO, treatment intervals may also be gradually extended, however there are insufficient data to conclude on the length of these intervals. ~~and central RVO (CRVO) or by one month at a time for DME and branch RVO (BRVO).~~ If disease activity recurs, the treatment interval should be shortened accordingly.

Special populations
Elderly
No dose adjustment is required in the elderly. There is limited experience in patients older than 75 years with DME.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Paediatric population
The warnings and precautions for adults also apply to preterm infants with ROP. Long-term safety in preterm infants with ROP has been studied for 2 years in the RAINBOW extension trial and showed no

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new safety signals. The ~~long-term~~ safety profile in preterm infants has not been established beyond 2 years.

Populations with limited data
There is only limited experience in the treatment of subjects with DME due to type I diabetes. Lucentis has not been studied in patients who have previously received intravitreal injections, in patients with active systemic infections, ~~proliferative diabetic retinopathy,~~ or in patients with concurrent eye conditions such as retinal detachment or macular hole. There is ~~also no~~limited experience of treatment with Lucentis in diabetic patients with an HbA1c over 108 mmol/mol (12%) and no experience in patients with uncontrolled hypertension. This lack of information should be con sidered by the physician when treating such patients.

4.8 Undesirable effects

Infections and infestations	
Common	~~Influenza,~~
Nervous system disorders	
~~*Common*~~	~~Stroke~~
Eye disorders	
Very common	~~Intraocular inflammation,~~

Paediatric population
Long-term safety in preterm infants with ROP has been studied for 2 years in the RAINBOW extension trial and showed no new safety signals. The ~~long-term~~ safety profile in preterm infants has not been established beyond 2 years.

5.1 Pharmacodynamic properties

Treatment of PDR
The clinical safety and efficacy of Lucentis in patients with PDR have been assessed in Protocol S which evaluated the treatment with ranibizumab 0.5 mg intravitreal injections compared with panretinal photocoagulation (PRP). The primary endpoint was the mean visual acuity change at year 2. Additionally, change in diabetic retinopathy (DR) severity was assessed based on fundus photographs using the DR severity score (DRSS).

Protocol S was a multicentre, randomised, active-controlled, parallel-assignment, non-inferiority phase III study in which 305 patients (394 study eyes) with PDR with or without DME at baseline were enrolled. The study compared ranibizumab 0.5 mg intravitreal injections to standard treatment with PRP. A total of 191 eyes (48.5%) were randomised to ranibizumab 0.5 mg and 203 eyes (51.5%) eyes were randomised to PRP. A total of 88 eyes (22.3%) had baseline DME: 42 (22.0%) and 46 (22.7%) eyes in the ranibizumab and PRP groups, respectively.

In this study, the mean visual acuity change at year 2 was +2.7 letters in the ranibizumab group compared to -0.7 letters in the PRP group. The difference in least square means was 3.5 letters (95% CI: [0.2 to 6.7]).

At year 1, 41.8% of eyes experienced a ≥2-step improvement in the DRSS when treated with ranibizumab (n=189) compared to 14.6% of eyes treated with PRP (n=199). The estimated difference between ranibizumab and laser was 27.4% (95% CI: [18.9, 35.9]).

Table 7 DRSS improvement or worsening of ≥2 or ≥3 steps at year 1 in Protocol S (LOCF Method)

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Categorised change from baseline	Protocol S		
	Ranibizumab 0.5 mg (N=189)	PRP (N=199)	Difference in proportion (%), CI
≥2-step improvement			
n (%)	79 (41.8%)	29 (14.6%)	27.4 (18.9, 35.9)
≥3-step improvement			
n (%)	54 (28.6%)	6 (3.0%)	25.7 (18.9, 32.6)
≥2-step worsening			
n (%)	3 (1.6%)	23 (11.6%)	-9.9 (-14.7, -5.2)
≥3-step worsening			
n (%)	1 (0.5%)	8 (4.0%)	-3.4 (-6.3, -0.5)
DRSS = diabetic retinopathy severity score, n = number of patients who satisfied the condition at the visit, N = total number of study eyes.			

At year 1 in the ranibizumab-treated group in Protocol S, ≥2-step improvement in DRSS was consistent in eyes without DME (39.9%) and with baseline DME (48.8%).

An analysis of year 2 data from Protocol S demonstrated that 42.3% (n=80) of eyes in the ranibizumab-treated group had ≥2-step improvement in DRSS from baseline compared with 23.1% (n=46) of eyes in the PRP group. In the ranibizumab-treated group, ≥2-step improvement in DRSS from baseline was observed in 58.5% (n=24) of eyes with baseline DME and 37.8% (n=56) of eyes without DME.

DRSS was also assessed in three separate active-controlled phase III DME studies (ranibizumab 0.5 mg PRN vs laser) that included a total of 875 patients, of whom approximately 75% were of Asian origin. In a meta-analysis of these studies, 48.4% of the 315 patients with gradable DRSS scores in the subgroup of patients with moderately severe non-proliferative DR (NPDR) or worse at baseline experienced a ≥2-step improvement in the DRSS at Month 12 when treated with ranibizumab (n=192) vs 14.6% of patients treated with laser (n=123). The estimated difference between ranibizumab and laser was 29.9% (95% CI: [20.0, 39.7]). In the 405 DRSS gradable patients with moderate NPDR or better, a ≥2-step DRSS improvement was observed in 1.4% and 0.9% of the ranibizumab and laser groups, respectively.

בהוראות השימוש:

Vial

Before withdrawal, ~~the outer part of the rubber stopper of the vial should be disinfected.~~ remove the vial cap and clean the vial septum (e.g. with 70% alcohol swab).

בעלון לצרכן:

1. למה מיועדת התרופה?

לטיפול ברטינופטיה סוכרתית שגשוגית (PDR)

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לוסנטיס מזהה ונקשרת באופן מובחן לחלבון הנקרא גורם גדילה הומני מסוג A של תאי אנדותל בכלי דם (VEGF-A) המצוי בעין. במצב של עודף, החלבון גורם לצמיחה לא תקינה של כלי דם ולנפיחות בעין שיכולות להוביל לליקוי בראיה, במחלות כמו ... ליקוי ראיה הנגרם כתוצאה מרטינופטיה סוכרתית שגשוגית (PDR), ...

4. תופעות לוואי

תופעות לוואי שכיחות (תופעות שמופיעות ב 1-10 משתמשים מתוך 100)

תופעות לוואי שאינן של הראיה כוללות: זיהום בדרכי השתן, ספירה נמוכה של כדוריות דם אדומות (עם תסמינים כגון עייפות, קוצר נשימה, סחרחורת, עור חיוור), חרדה, שיעול, בחילה, תגובות אלרגיות כמו פריחה, סרפדת, גרד והאדמה של העור, ~~שפעת, שבץ~~.

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