Choosing optimal pH range for product *Latanoprost + Netarsudil, 50 µg/ml + 200 µg/ml, eye drops, solution*

Odabir optimalnog pH raspona za proizvod *Latanoprost + Netarsudil, 50 µg/ml + 200 µg/ml, kapi za oči, otopina*

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Introduction

- Stress stability study was conducted to test optimal pH range for JGL product *Latanoprost + Netarsudil, 50 µg/ml + 200 µg/ml, eye drops, solution*.
- JGL product *Latanoprost + Netarsudil, 50 µg/ml + 200 µg/ml, eye drops, solution* (referred to as Test product) → indicated to lower elevated intraocular pressure (IOP) in adult patients with primary open-angle glaucoma or ocular hypertension for whom monotherapy with a prostaglandin or netarsudil provides insufficient IOP reduction.
- Reference medicinal product (RMP) is Roclanda with pH value set to approximately pH 5 [1].
- Test product and RMP were directly compared in previous stress stability studies (data not shown).

Stress study setup

- Formulation of Test product was manufactured with pH in range of 4.5 – 5.2 (**Figure 1**).
- Test products were kept at storage (2-8°C) and accelerated (25°C/60%RH) condition.
- Pull date of Test products was executed in four different intervals: T0 (day when products were placed on the stability study conditions), T14, T28, T45.
- Critical parameters analysed: appearance, pH, osmolality, buffer capacity, assay and impurities of latanoprost and netarsudil (**Table 1**).
- Main goal of this study was to confirm lower and upper value of the pH range, as well to set pH value at which drug product will be adjusted during manufacturing process of final product.

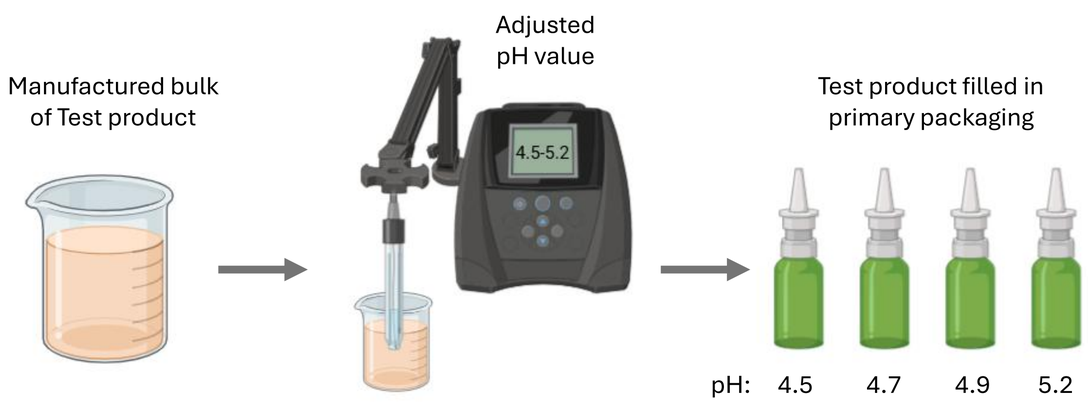

Figure 1. Scheme of Test product preparation

Table 1. Test products were compared by critical parameters

Parameter	Shelf-life requirements
Appearance	Clear, colourless solution, practically free from visible particles
pH	4.5 – 5.2
Osmolality	250 – 310 mOsmol/kg
Buffer capacity	Informative (mol/L)
Assay of latanoprost	95.0 – 105.0 %
Impurities of latanoprost: Impurity 1, Impurity 4, 15-keto latanoprost, Individual unspecified impurity, Total impurities (except impurity 4)	
Assay of netarsudil	95.0 – 105.0 %
Impurities of netarsudil: NEA-S2, NEA-S3, NEA-Impurity A, NEA-Impurity B, Individual unspecified impurity, Total impurities	

Results

Storage condition (2-8°C)

Data obtained for all tested parameters investigated on Test product samples with differently adjusted pH value comply to the set requirements in the drug product specification (**Figure 2-5**). No trends were observed for analysed parameters during stress stability study on followed intervals.

Accelerated condition (25°C/60%RH)

Analyses of all investigated parameters were in the range set in the drug product specification (**Figure 2-5**). Results for impurities of netarsudil, precisely individual unspecified impurity (RRT 1.258-1.260, **Figure 5**) and total impurities showed upward trend on intervals T28 and T45, and with increase of adjusted pH value, specifically in Test product sample with pH 5.2, although measured data were still in the range (shelf-life requirements) set in the drug product specification. Above-mentioned individual unspecified impurity of netarsudil with RRT 1.258-1.260 was under toxicological evaluation and newly proposed maximal value is 2.5%, instead of 1.0% (value set in the existing drug product specification), meaning observed upward trend has no impact on shelf-life requirement for final drug product (even after opening).

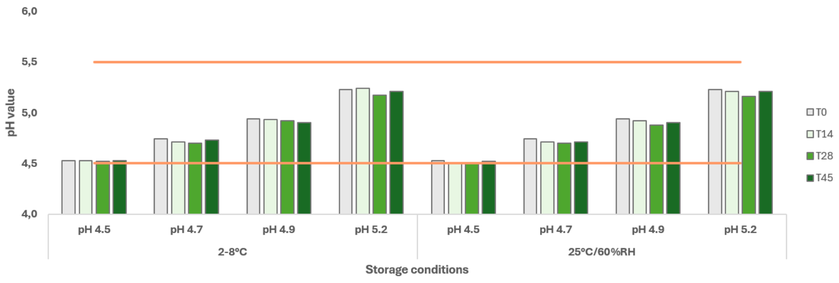

Figure 2. pH value measured during stress stability study at intervals T0, T14, T28 and T45 in Test product with differently adjusted pH value.

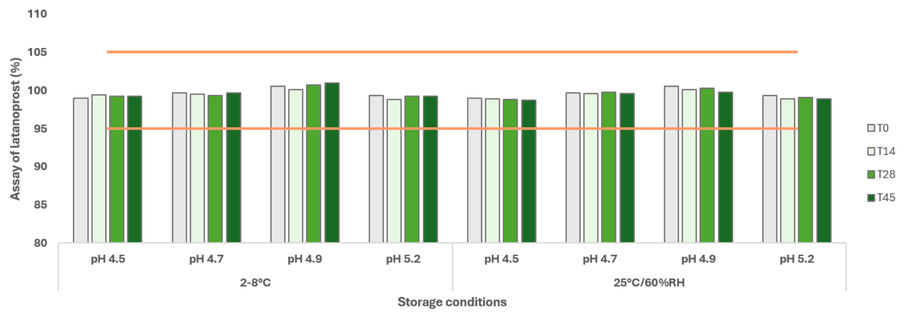

Figure 3. Assay of latanoprost measured during stress stability study at intervals T0, T14, T28 and T45 in Test product with differently adjusted pH value.

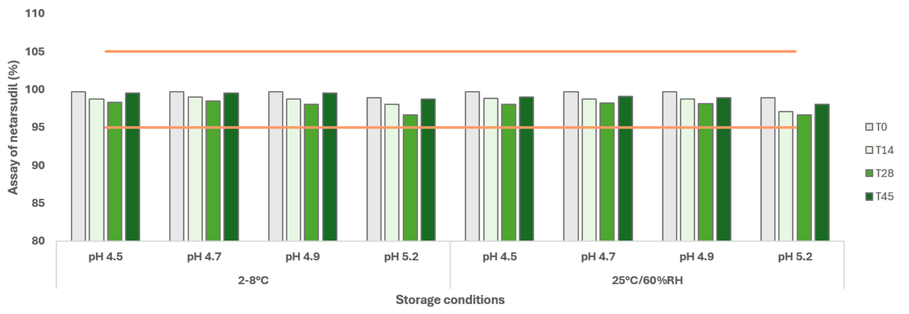

Figure 4. Assay of netarsudil measured during stress stability study at intervals T0, T14, T28 and T45 in Test product with differently adjusted pH value.

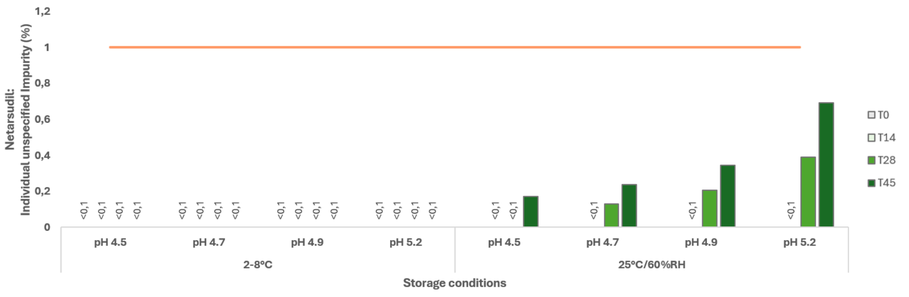

Figure 5. Content of individual unspecified impurity of netarsudil measured during stress stability study at intervals T0, T14, T28 and T45 in Test product with differently adjusted pH value.

Conclusion

Analysed parameters such as appearance, pH, osmolality, buffer capacity, assay of netarsudil, assay and impurities of latanoprost were stable during stress stability study in tested pH range. Study revealed that with increase in pH value in the solution of the final product, individual unspecified/total impurities of netarsudil show upward trend over period of time at 25°C/60%RH.

Key outcomes from this stability study:

- IPC requirement during manufacturing process will be set to pH range 4.7 – 4.9,
- Acceptance criteria for pH range throughout shelf-life period of Test product will be set to 4.5 – 5.2, what is additionally supported by literature due to netarsudil dimesylate precipitation above pH value of 5.4 [2].

Literature

[1] Roclanda | European Medicines Agency (EMA)

[2] Wang T, Zhang Y, Chi M, et al. A novel fixed-combination timolol-netarsudil-latanoprost ophthalmic solution for the treatment of glaucoma and ocular hypertension. *Asian J Pharm Sci*. 2022;17(6):938-948. doi:10.1016/j.ajps.2022.11.001

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