אוקטובר 2022

רופא/ה נכבד/ה, רוקח/ת נכבד/ה,

שלום רב,

הנדון : **LUTATHERA 370 MBq/ML SOLUTION FOR INFUSION**

חברת נוברטיס ישראל בע"מ מבקשת להודיע על עדכון העלון לרופא של התכשיר לוטאטרה.

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התוויות התכשיר:

Lutathera is indicated for the treatment of unresectable or metastatic, progressive, well differentiated (G1 and G2), somatostatin receptor positive gastroenteropancreatic neuroendocrine tumours (GEP NETs) in adults.

חומר פעיל:

LUTETIUM (177LU) OXODOTREOTIDE 370 MBQ/ML

בעמודים העוקבים מצויינים סעיפים בהם נעשה שינוי אשר מהווה החמרה במידע הבטיחות או שינוי משמעותי. למידע נוסף, יש לעיין בעלון לרופא. עלון לרופא מעודכן נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלו מודפס על-ידי פניה לבעל הרישום: נוברטיס ישראל בע"מ. תוצרת הארץ 6, ת"ד 7126, תל אביב.

בברכה,

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להלן פירוט שינויי הבטיחות העיקריים (טקסט באדום עם קו תחתי מציין טקסט שהוסף לעלון ואילו טקסט שהושמט מסומן באדום עם קו חוצה. החמרה במידע בטיחותי מודגשת בצהוב)

4.4 Special warnings and precautions for use

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Hypersensitivity

Cases of hypersensitivity reactions (including isolated angioedema events) have been reported in the post-marketing setting in patients treated with Lutathera (see section 4.8). In the event of serious hypersensitivity reactions, treatment with Lutathera should be discontinued immediately. Appropriate medicinal products and equipment to manage such reactions should be available for immediate use.

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4.8 Undesirable effects

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At the time of the NETTER-1 final analysis, after a median follow-up duration of 76 months in each study arm, the safety profile remained consistent with that previously reported.

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MedDRA System Organ Class (SOC)	Very common	Common	Uncommon	Not known
Immune system disorders			Hypersensitivity	Angioedema

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Therapeutic radiopharmaceuticals, Other therapeutic radiopharmaceuticals, ATC code: V10XX04

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Clinical efficacy and safety

NETTER-1 phase III study was a multicentre, stratified, open-label, randomized, comparator-controlled, parallel-group study comparing treatment with Lutathera (4 doses of 7,400 MBq every 8 weeks) co-administered with amino acid solution and best supportive care (BSC; octreotide long-acting release [LAR] 30 mg every 4 weeks for symptoms control, replaced by short-acting octreotide in the 4-weeks interval before Lutathera administration) to high-dose octreotide LAR (60 mg every 4 weeks) in patients with inoperable, progressive, somatostatin receptor-positive, midgut carcinoid tumours. The primary endpoint for the study was progression-free survival (PFS) evaluated by response evaluation criteria in solid tumours (RECIST 1.1), based on independent radiology assessment. Secondary endpoints included objective response rate (ORR), overall survival (OS), time to tumour progression (TTP), safety and tolerability of the medicinal product, and health-related quality of life (QoHRQoL).

At the time of the primary analysis, T~~wo hundred twenty-nine (~~229~~)~~ patients were~~have been~~ randomized to receive either Lutathera (n=116) or high-dose ~~60 mg~~ octreotide LAR (n=113). Demographics~~ as well as patients and~~ and baseline disease characteristics were well balanced between the treatment arms~~ groups~~ with a median age of 64 years and 82.1% Caucasian in the general population.

At the time of the primary PFS analysis ~~final per protocol PFS statistical analysis~~ (cut-off date 24 July 2015), the number of centrally confirmed disease progressions or deaths was 21 events in the Lutathera arm and 70 events in the high-dose octreotide LAR arm (Table 1~~Table 8~~). PFS differed significantly ($p<0.0001$) between the treatment ~~groups~~arms. The median PFS for the Lutathera arm was not reached at the cut-off date,~~time of analysis~~ whereas the median PFS for the ~~one of~~high-dose octreotide LAR arm was 8.5 months. The hazard ratio (HR) for the Lutathera arm compared to the high-dose octreotide LAR arm was 0.18 (95% CI: 0.11 - 0.29), indicating 82% reduction in the risk of disease progression or death in favour of the Lutathera arm.~~for a patient to progress or die under Lutathera compared to octreotide LAR.~~

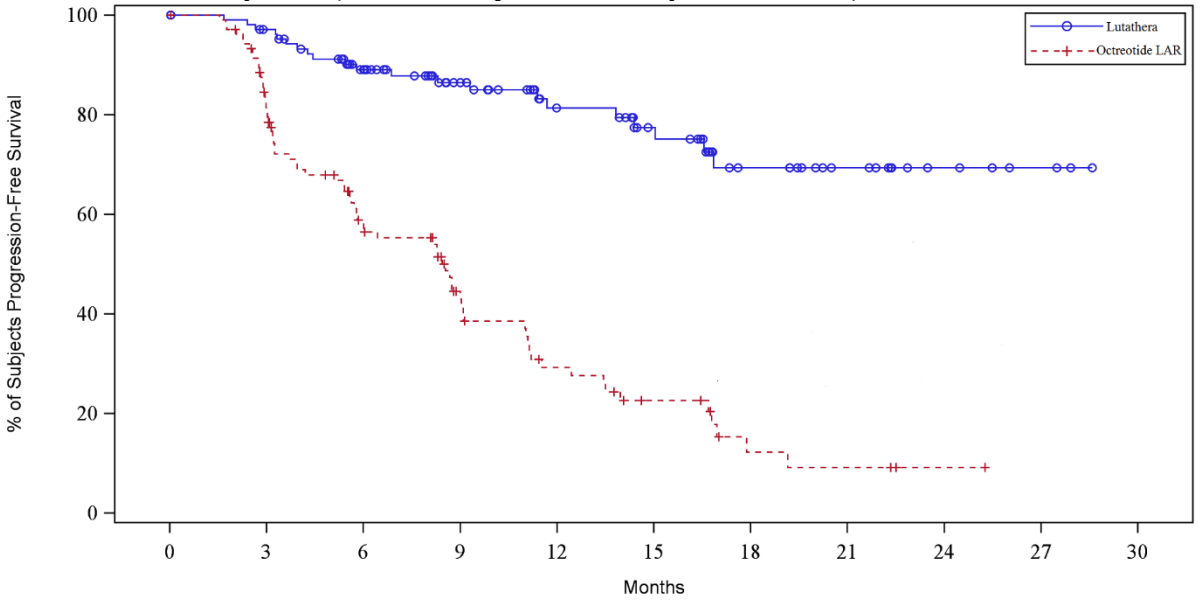
Table 18. PFS observed in the NETTER-1 phase III study in patients with progressive midgut carcinoid tumours – cut–off date 24 July 2015 (full analysies set [(FAS)], N=229)

	Treatment	
	Lutathera and octreotide LAR	**High-dose Ooctreotide LAR**
N	116	113
Patients with events	21	70
Censored patients	95	43
Median in months (95% -CI)	Not reached	8.5 (5.8-; 9.1)
p-value of Log-rank test	<0.0001	
Hazard ratio (95% -CI)	0.177 (0.108-; 0.289)	

N: number of patients, CI: confidence interval.

The PFS Kaplan-Meier graph for the full analysis set (FAS) at the cut–off date 24 July 2015 is depicted in Figure 1Figure 3.

Figure 13. PFS Kaplan--Meier curves of for patients with progressive midgut carcinoid tumours - cut–off date 24 July 2015 (NETTER-1 phase III study; FAS, N=229)



At the cut-off date for post-hoc statistical analysis (cut-off date 30 June 2016) including two additional randomised patients (N=231), the number of centrally confirmed disease progressions or deaths was 30 events in the Lutathera arm and 78 events in the high-dose octreotide LAR arm (Table 2Table 9). PFS differed significantly (p<0.0001) between the treatment groupsarms. The median PFS for the Lutathera arm was 28.4 months whereas the median PFS for theone of high-dose octreotide LAR arm was 8.5 months. The hazard ratio for the Lutathera arm compared to the high-dose octreotide LAR arm was 0.21 (95% CI: 0.14 - 0.33), indicating 79% reduction in the risk of disease progression or death in favour of the Lutathera armfor a patient to progress or die under Lutathera compared to octreotide LAR.

Table 29. PFS observed in the NETTER- 1 phase III study in patients with progressive midgut carcinoid tumours - cut-off date 30 June 2016 (full analyses set (FAS), N=231)

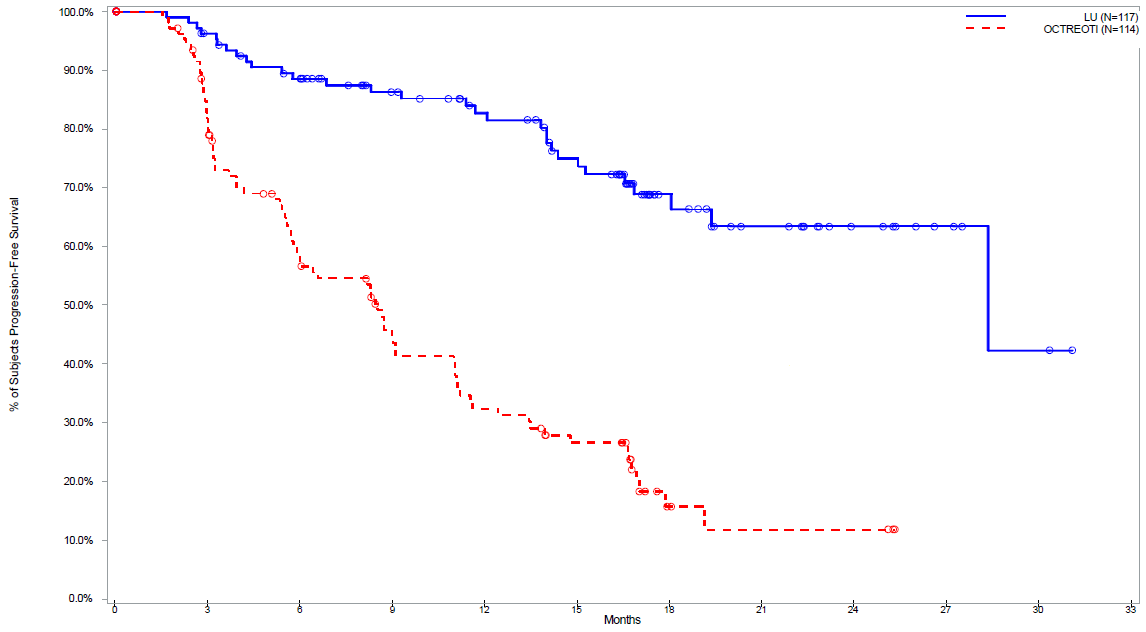
	Treatment	
	Lutathera and octreotide LAR	**High-dose Ooctreotide LAR**
N	117	114
Patients with events	30	78
Censored patients	87	36

Median in months (95%- CI)	28.4 (28.4; NE)	8.5 (5.8; 11.0)
p-value of Log-rank test	<0.0001	
Hazard ratio (95%- CI)	0.214 (0.139-; 0.331)	

N: number of patients, CI: confidence interval.

The PFS Kaplan-Meier graph for the full analysis set (FAS) at the cut-off date 30 June 2016 is depicted in Figure 2~~Figure 4~~.

Figure 24. PFS Kaplan--Meier curves ~~of~~ for patients with progressive midgut carcinoid tumours - cut-off date 30 June 2016 (NETTER-1 phase III study; FAS, N=231)



~~With respect to overall survival OS, at the time of interim analysis (24 July 2015), there were 17 deaths in the Lutathera arm and 31 in octreotide LAR 60 mg arm and the hazard ratio was 0.459 in favour of Lutathera, but did not reach the level of significance for interim analysis (HR 99.9915% CI: 0.140, 1.506). OS median was 27.4 months in octreotide LAR arm and was not reached in Lutathera arm. An update conducted about one year after (30 June 2016) showed similar trend with 28 deaths in the Lutathera arm and 43 in octreotide LAR 60 mg arm, an HR of 0.536, and a median OS of 27.4 months in octreotide LAR arm and still not reached in Lutathera arm. The final OS analysis is foreseen after 158 cumulative deaths.~~

At the time of the interim OS analysis (cut-off date 24 July 2015), there were 17 deaths in the Lutathera arm and 31 deaths in the high-dose octreotide LAR arm, yielding a HR of 0.459 (99.9915% CI: 0.140, 1.506) in favour of the Lutathera arm. The median OS was not reached in the Lutathera arm at the cut-off date, while it was 27.4 months in the high-dose octreotide LAR arm. The interim OS results did not reach statistical significance. An update conducted about one year later (cut-off date 30 June 2016) including two additional randomised patients (N=231) showed a similar trend with 28 deaths in the Lutathera arm and 43 deaths in the high-dose octreotide LAR arm, yielding a HR of 0.536 in favour of the Lutathera arm. The median OS was still not reached in the Lutathera arm at the cut-off date, while it was 27.4 months in the high-dose octreotide LAR arm.

At the time of the final OS analysis, which occurred 5 years after the last patient randomised (N=231, cut-off date 18 January 2021), the median follow-up duration was 76 months in each study arm. There were 73 deaths in the Lutathera arm (62.4%) and 69 deaths in the high-dose octreotide LAR arm (60.5%), yielding a HR of 0.84 (95% CI: 0.60, 1.17; unstratified Log-rank test p=0.3039, two-sided) in favour of the Lutathera arm. The median OS was prolonged by a clinically relevant extent of 11.7 months in patients randomised to the Lutathera arm compared to patients randomised to high-dose octreotide LAR, with a median OS of 48.0 months (95% CI: 37.4, 55.2) and 36.3 months

(95% CI: 25.9, 51.7), respectively. The final OS results did not reach statistical significance. In the high-dose octreotide LAR arm, 22.8% of patients received subsequent radioligand therapy (including lutetium (^{177}Lu) oxodotreotide) within 24 months of randomisation, and 36% of patients by the final OS cut-off date, which along with other factors may have influenced the OS in this subset of patients.

In presence of non-proportional hazards, an additional sensitivity analysis (Restricted mean survival time) was performed at the time of the final OS analysis to further estimate the treatment effect. At 60 months after randomisation, the average OS benefit was 5.1 months (95% CI: -0.5, 10.7) longer in the Lutathera arm compared to the high-dose octreotide LAR arm.

The OS Kaplan-Meier graph for the full analysis set (FAS) at the cut-off date 18 January 2021 is depicted in Figure 5.

Figure 5 OS Kaplan-Meier curves for patients with progressive midgut carcinoid tumours - cut-off date 18 January 2021 (NETTER-1 phase III study; FAS, N=231)

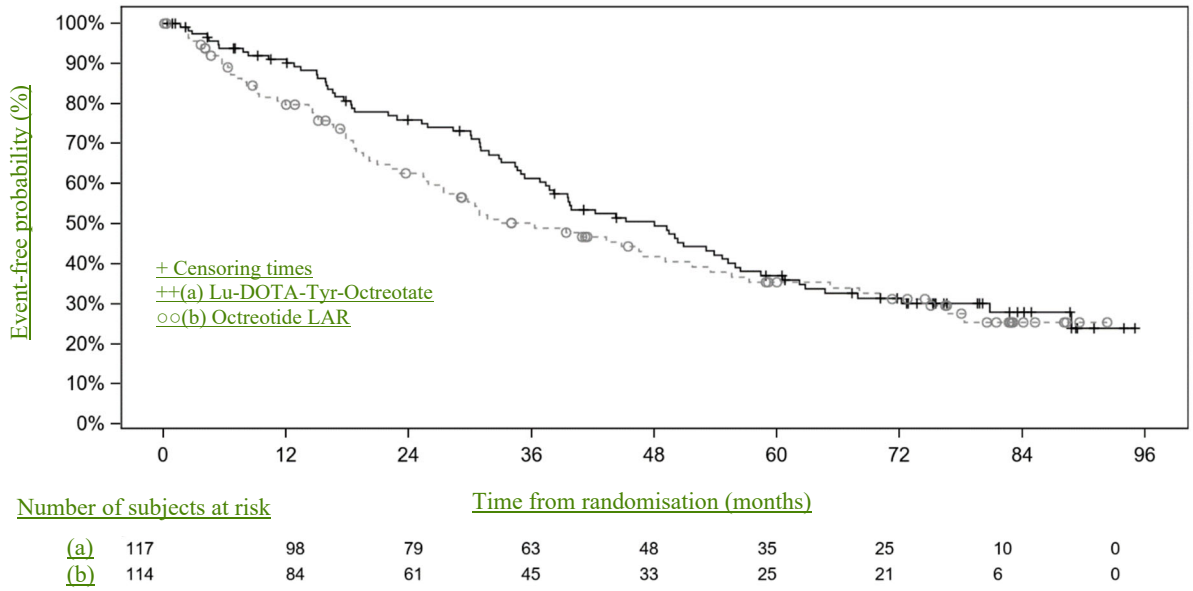


Table 10 OS by restricted mean survival time (RMST) observed in the NETTER-1 phase III study in patients with progressive midgut carcinoid tumours (FAS)

		Lutathera and octreotide LAR N=117	High-dose octreotide LAR N=114
24 months	Deaths, n (%)	26 (22.2)	39 (34.2)
	RMST (95% CI)	21.2 (20.2; 22.3)	19.3 (18.0; 20.7)
	Difference (95% CI)	1.9 (0.1; 3.6)	
36 months	Deaths, n (%)	41 (35.0)	51 (44.7)
	RMST (95% CI)	29.7 (27.7; 31.6)	26.0 (23.7; 28.3)
	Difference (95% CI)	3.7 (0.7; 6.7)	
48 months	Deaths, n (%)	53 (45.3)	58 (50.9)
	RMST (95% CI)	36.2 (33.4; 39.0)	31.5 (28.3; 34.8)
	Difference (95% CI)	4.6 (0.3; 8.9)	
60 months	Deaths, n (%)	65 (55.6)	63 (55.3)
	RMST (95% CI)	41.2 (37.6; 44.9)	36.1 (31.9; 40.4)
	Difference (95% CI)	5.1 (-0.5; 10.7)	

Health-Related Quality of Life (HRQOoL) was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (generic instrument) and its neuroendocrine tumour module (EORTC QLQ-GI.NET-21).

The results indicate an improvement in the overall global health-related quality of life up to week 84, for patients onin the Lutathera treatment arm as compared to patients on Oin the high-dose octreotide LAR arm.

The Erasmus phase I/II study was a monocentric single-arm open-label study to evaluate the efficacy of Lutathera (7,400 MBq administered for 4 times every 8 weeks) co-administered with amino acid solution in patients with somatostatin receptor-positive tumours. The mean age of patients enrolled in the study was 60 years. Most patients were Dutch (811) with the remaining (403) residents of various European and non-European countries. The main analysis has been conducted on 811 Dutch patients with different somatostatin receptor-positive tumour types. The ORR (including complete response ([CR]) and partial response ([PR]) according to RECIST criteria) and duration of response (DoR) for the FAS Dutch population with gastroenteropancreatic (GEP) and bronchial NETs (360 patients) as well as per tumour type are presented in Table 110.
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