VALSTYBINĖ VAISTŲ KONTROLĖS TARNYBA
PRIE LIETUVOS RESPUBLIKOS
SVEIKATOS APSAUGOS MINISTERIJOS

Lietuvos Respublikos Sveikatos apsaugos ministerijos Ligų, vaistinių preparatų ir medicinos pagalbos priemonių kompensavimo komisijai	Į	2017-10-23	Nr. Nr. SAM-S17-027

DĖL GAUTOS PAPILDOMOS MEDŽIAGOS VAISTINIAM PREPARATUI *CYRAMZA* (RAMUCIRUMABAS)

Valstybinė vaistų kontrolės tarnyba prie Lietuvos Respublikos sveikatos apsaugos ministerijos (toliau – Tarnyba) išnagrinėjo UAB "Eli Lilly Lietuva" (toliau Pareiškėjas) 2017 m. spalio 23 d. raštą ir pateiktą papildomą medžiagą dėl vaistinio preparato ramucirumabo (*Cyramza*) terapinės vertės, skiriant antraeiliam gydymui kartu su docetakseliu, suaugusiems pacientams, kuriems diagnozuotas lokaliai išplitęs arba metastazavęs nesmulkiųjų ląstelių plaučių vėžys, kai liga progresuoja po pirmesnės chemoterapijos, kurios pagrindą sudarė platinos preparatai.

Pirminės paraiškos metu, nustatyta ramucirumabo terapinė vertė buvo 10 balų (4+7-1). Vaistinis preparatas įvertintas kaip suteikiantis reikšmingą pridėtinę terapinę naudą pacientų, kurie gali būti gydomi nauju vaistiniu preparatu, pogrupiui. Terapinė nauda buvo sumažinta vienu balu, nes ramucirumabo ir docetakselio derinys buvo susijęs su toksiškumo padidėjimu, lyginant su placebu ir docetakseliu. Tai reikalauja papildomo gydymą skiriančių specialistų budrumo ir riziką mažinančių priemonių.

Pareiškėjas pateikė raštą, kuriame nesutinka su ramucirumabo terapinės vertės vertinimu.

Papildomai pateikta medžiaga:

1. Paraiškos lentelė su atnaujintomis ES kainomis (vienas lapas).

Priede Nr. 1 nurodoma informacija apie kainas įtakos terapinei vertei neturi.

Pareiškėjo teigimu, balas už saugumo profilį, neturėtų būti atimtas, nes ramucirumabo saugumas atitinka chemoterapinių vaistų saugumo reikalavimus, o nepageidaujamos reakcijos REVEL tyrimo metu buvo lengvai kontroliuojamos sumažinus ramucirumabo dozes. Tačiau naujų duomenų ar klinikinių tyrimų nebuvo pateikta. Ramucirumabo terapinė vertė lieka nepakitusi.

Žemiau lentelėje pateikiami kitų šalių agentūrų vertinimai:

SMC (Škotija)	Ramucirumab (*Cyramza*) **is not recommended** for use within NHS Scotland. The holder of the marketing authorisation **has not made a submission** to SMC regarding this product in this indication. https://www.scottishmedicines.org.uk/media/2212/dad_ramucirumab_cyramza_non-_sub__final_may_2016_for_website.pdf
HAS	The Commission notes <…> that CYRAMZA is not refundable in the indication:

(Prancūzija)	"in combination with docetaxel, in the treatment adult patients with locally advanced or metastatic non-small cell lung cancer whose disease has progressed after platinum-based chemotherapy ". https://www.has-sante.fr/portail/upload/docs/evamed/CT-15353_CYRAMZA_cancer_bronchique_avanc%C3%A9_PIS_EI_non_demand%C3%A9e_Avis2_CT15353.pdf
CADTH (Kanada)	The submitter notified pCODR that they will not be filing the submission. https://cadth.ca/cyramza-non-small-cell-lung-cancer-details
NICE (Jungtinė Karalystė)	Ramucirumab, in combination with docetaxel, is **not recommended** within its marketing authorisation for treating locally advanced or metastatic non-small-cell lung cancer (NSCLC) in adults whose disease has progressed after platinum-based chemotherapy. The committee concluded that **ramucirumab plus docetaxel was more effective** than docetaxel alone based on the results of the REVEL trial and similar in eficacy to nintedanib plus docetaxel based on a network meta-analysis. The committee concluded that the most plausible ICERs were well over the range that would normally be considered a cost-effective use of NHS resources. The committee concluded that ramucirumab plus docetaxel met the NICE supplementary advice criteria to be considered as a **life-extending, end-of-life** treatment only for the population with non-squamous disease, when ramucirumab plus docetaxel is compared with docetaxel alone. The committee heard from the clinical and patient experts that there were few options for treating NSCLC with no positive tumour marker and that ramucirumab would provide another option. However, the committee concluded that having an extra treatment option for NSCLC did not mean that ramucirumab was innovative. https://www.nice.org.uk/guidance/ta403/resources/ramucirumab-for-previously-treated-locally-advanced-or-metastatic-nonsmallcell-lung-cancer-pdf-82604541080005
IQWIG (Vokietija)	• Severe adverse events (CTCAE grade ≥ 3): A statistically significant difference to the disadvantage of ramucirumab + docetaxel versus docetaxel was shown here. This resulted in a **hint of greater harm of** ramucirumab + docetaxel in comparison with docetaxel for this outcome. • Discontinuation due to adverse events: The meta-analysis of the included studies showed a **statistically significant difference to the disadvantage** of ramucirumab + docetaxel versus docetaxel for the outcome “discontinuation due to AEs”. This resulted in proof of greater harm of ramucirumab + docetaxel in comparison with docetaxel for this outcome. • Specific adverse events: stomatitis (CTCAE grade ≥ 3) and febrile neutropenia (CTCAE grade ≥ 3): The meta-analysis of the included studies showed a **statistically significant difference to the disadvantage** of ramucirumab + docetaxel in comparison with docetaxel for each of the AE outcomes “stomatitis” (CTCAE grade ≥ 3) and “febrile neutropenia” (CTCAE grade ≥ 3). There was an indication of **greater harm for the outcome “stomatitis” (CTCAE grade ≥ 3**) and proof of **greater harm for the outcome “febrile neutropenia” (CTCAE grade ≥ 3),** in each case from ramucirumab + docetaxel in comparison with docetaxel. • Specific adverse events: bleeding/haemorrhagic events: The meta-analysis of the included studies showed a **statistically significant difference to the disadvantage** of ramucirumab + docetaxel in comparison with docetaxel for the outcome “bleeding/haemorrhagic events”. **Patients < 65 years:** In the overall consideration, there were positive and negative effects for patients <

	65 years. On the positive side, there was proof of an added benefit of **considerable extent for the outcome "overall survival**" and a hint of lesser harm of considerable extent in the outcome category "SAEs". The positive effects were accompanied by negative effects with different extent and different certainty of results. A hint of greater harm with minor extent (severe AEs CTCAE grade ≥ 3), an indication of greater harm of considerable extent (stomatitis CTCAE grade ≥ 3), and proof of greater harm also of considerable extent (febrile neutropenia CTCAE grade ≥ 3) were found in the category "serious/severe side effects". In addition, there were further negative effects in the category "non-serious/non-severe side effects". Overall, the negative effects were not so large as to completely outweigh the mortality advantage of ramucirumab in combination with docetaxel. In summary, there is proof of a **minor added benefit** of ramucirumab in combination with docetaxel versus the ACT docetaxel for the subgroup of patients < 65 years. **Patients ≥ 65 years:** For patients ≥ 65 years, only negative effects remained in the outcome categories "serious/severe side effects" and "non-serious/non-severe side effects", which were of minor and considerable extent with different probabilities (hint, indication, or proof). In summary, there is therefore **proof of lesser benefi**t of ramucirumab in combination with docetaxel versus the ACT docetaxel for the subgroup of patients ≥ 65 years. https://www.iqwig.de/en/press/press-releases/ramucirumab-in-colorectal-and-lung-cancer-partly-added-benefit-partly-lesser-benefit.7374.html

Viršininkas Gintautas Barcys