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 2017-10-27	Nr. Nr. (1.18)3R-18676

DĖL GAUTOS PAPILDOMOS MEDŽIAGOS VAISTINIAM PREPARATUI LARTRUVO (OLARATUMABAS)

Valstybinė vaistų kontrolės tarnyba prie Lietuvos Respublikos sveikatos apsaugos ministerijos (toliau – Tarnyba) išnagrinėjo UAB "Eli Lilly Lietuva" (toliau Pareiškėjas) 2017 m. spalio 27 d. raštą ir pateiktą papildomą medžiagą dėl vaistinio preparato olaratumabo (*Lartruvo*) terapinės vertės.
Pirminės paraiškos metu, nustatyta olaratumabo terapinė vertė buvo 10 balų (4+7-1). Vaistinis preparatas įvertintas kaip suteikiantis pridėtinę terapinę naudą daliai pacientų, kurie gali būti gydomi nauju vaistiniu preparatu. Terapinė nauda buvo sumažinta vienu balu, nes olaratumabo ir doksorubicino derinys sukelia daugiau reikšmingų nepageidaujamų poveikių, nei vienas doksorubicinas, ir vaisto efektyvumas ir saugumas nėra galutinai ištirtas – vaistas įregistruotas su sąlyga, kad bus atliktas tolesnis efektyvumo ir saugumo stebėjimo tyrimas.

Pareiškėjas pateikė papildomą medžiagą ir raštą, kuriame nesutinka su nustatyta terapine verte.

Papildomai pateikta medžiaga:

1. Paraiškos lentelė su atnaujintomis ES kainomis (du lapai);
2. Lentelė 1. Summary of AE Occuring in >10% of Patients in Any One Arm (Any Grade) (Safety Population), study JGDG (vienas lapas);
3. Lentelė 2. Incidence of Grade >3 AE That Occured in >5% in Any One Arm (Safety Population), study, JGDG (vienas lapas);
4. Lentelė 3. Discontinuations Due to SE (Safety Population), study JGDG (vienas lapas);
5. Lentelė 4. Hospitalizations (Safety Population), study JGDG (vienas lapas);
6. Lentelė 5. Overall Survival by Exposure to Doxorubicin, Study JGDG, phase 2; ITT Population (vienas lapas).

Registruota olaratumabo (*Lartruvo*) indikacija:
Lartruvo skirtas vartoti kartu su doksorubicinu išplitusiai minkštųjų audinių sarkomai gydyti suaugusiems, doksorubicinu negydytiems pacientams, kuriems neįmanoma atlikti chirurginę operaciją ar skirti spindulinį gydymą.

Pareiškėjo teigimu, balas už saugumą, neturėtų būti atimtas bei terapinė nauda turėtų būti vertinama 10 balų – vaistinis preparatas suteikia reikšmingą pridėtinę terapinę naudą daugumai pacientų, kurie gali būti gydomi nauju vaistiniu preparatu. Tačiau naujų duomenų ar klinikinių tyrimų Pareiškėjas nepateikė. Priede nr. 1 pateikta informacija apie kainas įtakos terapinei naudai

neturi. Pateiktuose prieduose (2, 3, 4, 5, 6) yra lentelės, kuriose pateikiami jau pirminėje paraiškoje vertinto klinikinio tyrimo (JGDG) rezultatai, naujų duomenų nepateikta. Dvigubai aklo III fazės placebu kontroliuojamo klinikinio tyrimo (ANNOUNCE) rezultatų laukiama 2019 metais. Olaratumabo terapinė vertė lieka nepakitusi.

Žemiau lentelėje pateikiami kitų šalių agentūrų vertinimai:

SMC (Škotija)	SMC restriction: for use in combination with doxorubicin as **first-line** treatment for advanced soft-tissue sarcoma not amenable to curative treatment with surgery or radiotherapy. **Surgery** is the recommended treatment where possible and is potentially the **only curative option.** Radiotherapy may be used, however it has no effect on cure rates. In patients with advanced or metastatic disease, treatment is likely to be **palliative** and **doxorubicin is considered first-line** standard of care with a response rate of 10% to 30%. The **addition of ifosfamide to first-line doxorubicin** treatment is associated with a higher response rate, however it also has a higher risk of toxicity and has not been shown to have an overall survival (OS) benefit. Ifosfamide may also be used first-line where anthracyclines are contra-indicated. The potential cardiac toxicity of doxorubicin and renal toxicity with ifosfamide means that patients' performance status and comorbidities are important considerations in choice of treatment. There is **unmet need** in this therapeutic area, namely first line treatment of advanced soft-tissue sarcoma. There were no patient-reported or quality of life outcomes. **The addition of olaratumab to doxorubicin therapy may increase the frequency of certain adverse events** associated with doxorubicin therapy, particularly nausea, neutropenia, anaemia, thrombocytopenia and alopecia. Musculoskeletal pain occurred more frequently in patients who received olaratumab; in most patients the pain was related to the underlying cancer and appeared to be limited to the first four to five cycles of treatment. Pain can adversely affect quality of life and pain control is a key concern in palliative treatment. Clinical experts consulted by SMC considered that **olaratumab is a therapeutic advancement due to the lack of alternative treatments** and the improvement in PFS and OS demonstrated in the study. They felt that the **place in therapy is in first line** treatment of advanced soft-tissue sarcoma in patients who are not amenable to curative treatment with surgery or radiotherapy. https://www.scottishmedicines.org.uk/media/3116/olaratumab_lartruvo_final_oct_2017_for_website.pdf
HAS (Prancūzija)	Nėra duomenų https://www.has-sante.fr/portail/jcms/c_39085/en/recherche?portlet=c_39085&text=oralatumab&opSearch=&lang=en&portal=c_2566858
CADTH (Kanada)	Išvadas planuojama pateikti 2018 m. kovo 29 d. https://cadth.ca/lartruvo-advanced-soft-tissue-sarcoma-details
NICE (Jungtinė Karalystė)	Olaratumab, in combination with doxorubicin, **is recommended** for use within the Cancer Drugs Fund as **an op**tion for advanced soft tissue sarcoma in adults, only if: - they have not had any previous systemic chemotherapy for advanced soft tissue sarcoma - they cannot have curative treatment with surgery or their disease does not respond to radiotherapy - the conditions in the managed access agreement for olaratumab are followed. Olaratumab plus doxorubicin met NICE's criteria to be considered a life-extending treatment at the **end of** life. The criteria are that life expectancy for people with the condition should be less than 24 months and that the treatment should extend life by more than 3 months. More long-term data would reduce uncertainty in the clinical effectiveness of olaratumab plus doxorubicin and allow a more certain cost effectiveness estimate. The **ongoing ANNOUNCE trial** is expected to address the uncertainty in the data. Olaratumab is therefore recommended for use within the Cancer Drugs Fund while further data are collected. The clinical experts agreed with the company's proposal that olaratumab in combination with doxorubicin **is likely to replace doxorubicin alone** as first-line treatment for people who have not had any previous systemic chemotherapy for advanced soft tissue sarcoma and cannot have curative treatment with surgery, or their disease does not respond to radiotherapy. Olaratumab plus doxorubicin was associated with an overall survival gain of 11.8 months compared with doxorubicin alone in JGDG, and concluded that it **met the extension-to-life criterion.** https://www.nice.org.uk/guidance/ta465/resources/olaratumab-in-combination-with-doxorubicin-for-

	treating-advanced-soft-tissue-sarcoma-pdf-82604907236293
IQWIG (Vokietija)	Orfaninis vaistas, terapinė nauda nevertinama. https://www.iqwig.de/en/projects-results/projects/health-economic/g16-13-olaratumab-sarcoma-assessment-according-to-35a-para-1-sentence-10-social-code-book-v.7741.html
TLV (Švedija)	The efficacy and safety of Lartruvo in combination with doxorubicin has been evaluated in a randomized open-phase 2 study in comparison with doxorubicin as monotherapy. In the study, Lartruvo, in combination with doxorubicin, produced a statistically significant improvement in survival compared to doxorubicin only, 26.5 months in the median versus 14.7 months in the median, with a risk ratio of 0.46. An improved progression-free survival in the median was given by Lartruvo in combination with doxorubicin, 6.6 months, compared to 4.1 month for the control arm, with a hazard ratio of 0.67. The uncertainty in the results is medium and mainly focuses on the long-term effects of Lartruvo treatment and the benefits that the company uses for the various health conditions in the health-economic model. • In the TLV's basic scenario, the cost per won QALY for Lartruvo in combination with doxorubicin is estimated at 940,000 kronor compared to doxorubicin monotherapy. • In TLV's basic scenario, the cost per won QALY for Lartruvo in combination with doxorubicin is estimated at 830,000 kronor compared to doxorubicin in combination with ifosfamide. https://tlv.se/ovriga-sidor/sok.html?query=olaratumab&submitButton=S%C3%B6k

Viršininkas Gintautas Barcys