

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final appraisal determination

**Olaratumab in combination with doxorubicin
for treating advanced soft tissue sarcoma**

1 Recommendations

1.1 Olaratumab, in combination with doxorubicin, is recommended for use within the Cancer Drugs Fund as an option 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.

1.2 This recommendation is not intended to affect treatment with olaratumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

People with advanced soft tissue sarcoma having doxorubicin alone are expected to live for 12 to 16 months after starting treatment. Evidence suggests that having olaratumab plus doxorubicin increases the length of time people live by 11.8 months. This amount of survival gain in advanced

sarcoma is unprecedented and potentially represents a step-change in its treatment. However, there is not enough long-term data to know the overall length of time people having olaratumab plus doxorubicin live compared with doxorubicin alone because the trial is still ongoing.

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.

The estimate of the cost effectiveness of olaratumab plus doxorubicin varied primarily because of the uncertainties in the data. The incremental cost-effectiveness ratios (ICERs) ranged between £46,000 and £60,000 per quality-adjusted life year (QALY) gained. The most plausible ICER is likely to be close to £60,000 per QALY gained. This is not cost effective based on what NICE normally considers acceptable for end-of-life treatments.

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.

2 The technology

Olaratumab (Lartruvo, Eli Lilly)	
Marketing authorisation/anticipated marketing authorisation	Olaratumab 500 mg has been granted a conditional marketing authorisation for the ‘treatment of adult patients with advanced soft tissue sarcoma who are not amenable to curative treatment with surgery or radiotherapy and who have not been previously treated with doxorubicin’.
Recommended dose and schedule	The recommended dose of olaratumab is 15 mg/kg, given by intravenous infusion on days 1 and 8 of each 3-week cycle until disease progression or unacceptable toxicity.

	<p>Olaratumab is given with doxorubicin for up to 8 cycles of treatment, followed by olaratumab alone in patients whose disease has not progressed.</p> <p>Doxorubicin is given on day 1 of each cycle, after the olaratumab infusion.</p>
Price	<p>As part of the managed access agreement, the company has a commercial access agreement with NHS England. This makes olaratumab available at a reduced cost. The financial terms of the agreement are commercial in confidence.</p>

3 Committee discussion

The appraisal committee (section 7) considered evidence submitted by Eli Lilly and a review of this submission by the evidence review group (ERG). See the [committee papers](#) for full details of the evidence.

Clinical need

Patients and clinicians would welcome a new, effective treatment for soft tissue sarcoma

3.1 A patient expert explained that because soft tissue sarcoma is rare, it may at first be confused with benign conditions and there are often delays in reaching the correct diagnosis. Soft tissue sarcoma, especially when unsuitable for surgery or which does not respond to radiotherapy, can have a profound effect on physical and psychological wellbeing, and may place both financial and emotional strain on patients, families and friends . Many people with the disease are of working age with carer responsibilities. The Cancer Drugs Fund clinical lead stated that olaratumab is the first effective treatment for soft tissue sarcoma in 25 years and the clinical experts considered it to be a step-change in the management of the condition. The committee heard from a clinical expert that although the potential overall survival benefit of olaratumab is obviously important, a longer time in stable (or even progressive) disease was also beneficial because people with soft tissue sarcoma can have a

good quality of life even when the disease is progressing. The committee concluded that both patients and clinicians would welcome the availability of a new, effective treatment for soft tissue sarcoma.

Clinical management

Olaratumab would be used first line and doxorubicin is the most relevant comparator

3.2 The committee heard from the clinical experts that doxorubicin alone is the current standard of care for soft tissue sarcoma in people who cannot have surgery, or whose disease does not respond to radiotherapy. However, doxorubicin is associated with low response rates of between 10% and 36%. Treatment at this stage aims to extend long-term survival, avoid local recurrence, maximise function and minimise morbidity. The clinical experts explained that multi-agent chemotherapy with ifosfamide and doxorubicin is rarely used because there is no evidence of an overall survival benefit compared with doxorubicin alone. 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 soft tissue sarcoma and cannot have curative treatment with surgery, or their disease does not respond to radiotherapy. The committee therefore concluded that olaratumab plus doxorubicin should be appraised as a first-line treatment for advanced soft tissue sarcoma, and that doxorubicin is the most relevant comparator.

The JGDG trial and clinical practice

The JGDG trial is broadly generalisable to clinical practice in England but further data would be helpful

3.3 The clinical evidence for olaratumab plus doxorubicin is from the JGDG (2016) trial, which was an open-label multicentre study of 133 people with advanced soft tissue sarcoma not amenable to treatment with surgery or

radiotherapy. People were randomised to have either olaratumab plus doxorubicin or doxorubicin alone for up to 8 cycles. In the trial, 65% of people had no previous systemic chemotherapy and none had previously had doxorubicin. The committee considered the level of heterogeneity in the trial population. It heard from the clinical experts that imbalances in the subtypes of soft tissue sarcoma and the baseline characteristics between the arms of the trial were unavoidable because of the rarity of the disease. The committee concluded that it had no reason to suppose that the trial population would not be representative of people seen in clinical practice in England. However it welcomed the possibility of further data collected through the Cancer Drugs Fund, which would be beneficial for future decision-making.

Additional doxorubicin treatment in the JGDG trial is not likely to impact the effectiveness of olaratumab in clinical practice

3.4 People in the JGDG trial had up to 8 cycles of doxorubicin, with the cardioprotective agent dexrazoxane from cycle 5 onwards. The Cancer Drugs Fund clinical lead representative explained that in UK clinical practice, patients are restricted to 6 cycles of doxorubicin. The clinical experts and the NHS England representative agreed that the additional cycles of doxorubicin in the trial were unlikely to have a large effect on the efficacy of olaratumab compared with doxorubicin. The committee also noted that dexrazoxane is not used in the NHS and concluded that it would not be needed for patients in clinical practice in the UK.

Overall and progression-free survival

Olaratumab has a modest effect on progression-free survival

3.5 In the JGDG trial, olaratumab plus doxorubicin increased median progression-free survival in the intention-to-treat population by 2.5 months compared with doxorubicin alone (olaratumab plus doxorubicin 6.6 months, doxorubicin alone 4.1 months; hazard ratio [HR] 0.73; 95% confidence interval [CI] 0.44 to 1.02 p= 0.06). The committee noted that

the results were similar for the subpopulation of people who had no previous systemic chemotherapies, which was 65% of the trial population (HR 0.77; 95% CI 0.48 to 1.25 p=0.28). The committee concluded that olaratumab was associated with an improvement in progression-free survival in both the intention-to-treat and in the subpopulation of people who had no previous systemic chemotherapies, and that the trial data were mature.

Olaratumab improves overall survival but the data are immature

3.6 In the JGDG trial, olaratumab plus doxorubicin increased median overall survival in the intention-to-treat population by 11.8 months compared with doxorubicin alone (olaratumab plus doxorubicin 26.5 months, doxorubicin alone 14.7 months; stratified HR 0.46; 95% CI 0.30 to 0.71 p=0.00). The results were similar in the subpopulation of people who had no previous systemic chemotherapies (stratified HR 0.47; 95% CI 0.27 to 0.81 p=0.00). The committee noted that the overall survival data are immature, but the overall survival gain appeared to be much greater than the progression-free survival gain. It considered the clinical plausibility of a progression-free survival benefit of 2.5 months translating into an overall survival benefit of 11.8 months. It discussed the potential relationship between progression-free and overall survival but, given the immaturity of the survival data, it agreed that the relationship is unclear. It noted that the ANNOUNCE trial is in progress, which is a multi-centre randomised, double-blind, placebo-controlled study. ANNOUNCE is expected to address key areas of clinical uncertainty in the JGDG trial. The committee concluded that although olaratumab demonstrated an improvement in overall survival, the data are immature and further data from the ANNOUNCE trial would confirm the long-term overall survival benefit of olaratumab plus doxorubicin.

Adverse events

Olaratumab has an acceptable adverse-event profile

- 3.7 There were more adverse events in the olaratumab plus doxorubicin arm of JGDG than in the doxorubicin-alone arm. This may relate to the higher cumulative dose of doxorubicin in the olaratumab plus doxorubicin arm compared with doxorubicin monotherapy (median 7.1 cycles and 4.1 cycles respectively). The committee heard from the clinical and patient experts that olaratumab seems to be very well-tolerated. They explained that in ANNOUNCE, based on the adverse-event profile, it is difficult for either patients or clinicians (who are blinded to treatment allocation) to tell whether people in the ANNOUNCE were having olaratumab plus doxorubicin or doxorubicin alone. The committee concluded that olaratumab plus doxorubicin has an acceptable adverse-event profile.

Economic model structure

The structure of the company's economic model was appropriate

- 3.8 The company used a cohort-based partitioned survival model to estimate the cost effectiveness of olaratumab plus doxorubicin compared with doxorubicin alone. The model population was adults with advanced soft tissue sarcoma not amenable to curative treatment (that is, who cannot have surgery or whose disease does not respond to radiotherapy) and who had not previously had doxorubicin. The model incorporated a confidential, provisional commercial access agreement. The committee considered the modelling of olaratumab as a first-line treatment to be appropriate. The model included 3 health states: progression-free survival, post-progression survival and death. Patients whose disease progressed had up to 3 further lines of therapy and best supportive care. The company also provided a model with ifosfamide and doxorubicin as the comparator. The committee concluded that the model comparing olaratumab plus doxorubicin with doxorubicin alone is most relevant to clinical practice (section 3.2), and did not consider the ifosfamide and doxorubicin model any further.

Extrapolation of survival data

The company's modelling of progression-free survival was acceptable

3.9 The company modelled progression-free survival using Kaplan–Meier analysis of the JGDG data. No extrapolation was done because the progression-free survival data were mature. The committee heard from the ERG that it agreed with the choice of Kaplan–Meier curves for the base-case analysis. The committee concluded that the company's modelling of progression-free survival was acceptable for the purposes of its decision-making.

The ERG's modelling of overall survival is more plausible than the company's model

3.10 The committee recalled that the data on overall survival from JGDG are immature. The company extrapolated patient survival up to 25 years, based on a mean age at diagnosis of 58.5 years in JGDG. Because of the small number of patients and events in the subpopulation of people who had no previous systemic chemotherapies, the company fitted parametric survival models to the intention-to-treat data set with line of therapy as a covariate. It used external observational data by Van Glabbeke et al. (1999) to validate the overall-survival data for patients having doxorubicin alone. The company considered the gamma distribution to be most appropriate for extrapolating overall survival, which predicted a 10-year survival of around 11% in the olaratumab plus doxorubicin arm and 5% in the doxorubicin-alone arm. The ERG commented that patients in the Van Glabbeke et al. study were substantially younger than those in JGDG (75.5% of patients were 60 years or younger), so using these data may overestimate long-term survival and give optimistic cost-effectiveness results. The ERG considered that a log-normal distribution provides a more clinically reasonable prediction of 10-year survival in this patient population: this predicted 10-year survival rates of 4.3% and 1.7% for olaratumab plus doxorubicin and doxorubicin alone respectively. The

clinical experts agreed that the company's predicted 10-year survival rate of 5% with doxorubicin alone was implausible. The committee concluded that the extrapolation of survival was uncertain, and that the ERG's log-normal extrapolation is more clinically plausible.

Utility values

The committee accepted the utility values used by the company

3.11 The JGDG trial did not include any health-related quality-of-life data, so the company did a systematic literature review to identify published health-state utility estimates. It considered 3 studies that provided consistent utility estimates, which were either directly measured using the EQ-5D or by mapping the EORTC-QLQ-C30 to the EQ-5D. Utility values in the company's base case were 0.72 in the pre-progression state and 0.56 in the post-progression state. These were based on a study by Reichardt et al. (2012), which reported health state utility values for patients with metastatic soft tissue and bone sarcoma that responded to chemotherapy. The mean age of patients at metastatic disease diagnosis in this study was 49.5 years, compared with 56.8 years and 58.3 years in the olaratumab plus doxorubicin and doxorubicin-alone arms of JGDG respectively. The ERG commented that because patients in Reichardt et al. were substantially younger than those in JGDG, utility may have been overestimated in the olaratumab model which would underestimate the ICER. The committee recognised the uncertainty in the utility values used in the model, which add to the uncertainty in the cost-effectiveness results. The committee therefore concluded that it would have preferred utility measurements directly from JGDG, but that in their absence the utility estimates used in the company model were acceptable for its decision-making.

Economic model costs

Olaratumab plus doxorubicin is most likely to be given as a day-case treatment

3.12 The committee noted that the company's and ERG's estimates of administration costs differed. The NHS England representative advised that administering olaratumab plus doxorubicin (including premedication for both) takes 2.5 to 3.0 hours, and that administering olaratumab alone (including premedication) takes up to 1.5 hours. The committee considered that the ERG's approach was more reflective of UK clinical practice. It concluded that olaratumab plus doxorubicin as a day-case treatment is more appropriate, and that the company's estimate was likely to underestimate the administration costs.

Administration costs in the company and ERG models were based on mean patient weights, but these are uncertain in clinical practice

3.13 The company assumed a mean patient weight of 77.3 kg, based on the GeDDis (2015) trial.

- For olaratumab plus doxorubicin, the company assumed a log-normal distribution around the mean weight of patients, and then used the JGDG mean dosage to estimate a weighted mean per-administration cost based on the proportion of patients that would have the relevant combination of vial sizes.
- For doxorubicin alone, the company assumed a log-normal distribution around the mean weight of patients, and then estimated a weighted per-administration based on the proportion of patients that would have the relevant combination of vial sizes.

The ERG considered the mean patient weights in JGDG to be more appropriate (85.5 kg in the olaratumab plus doxorubicin arm and 82.5 kg in the doxorubicin-alone arm). The committee acknowledged this but noted that the weight of patients with advanced soft tissue sarcoma in clinical practice in general was uncertain, and concluded that the company's approach was acceptable.

The company's base-case ICER is likely to be an underestimate

3.14 The company's base-case incremental cost-effectiveness ratio (ICER) for olaratumab plus doxorubicin compared with doxorubicin alone, using the discounted price for olaratumab in the commercial access scheme, was £46,076 per quality-adjusted life year (QALY) gained. The ERG's base-case ICER which used the same utility values as in the company model was higher, particularly because of the way overall survival was extrapolated, but also related to its assumption of day-case administration and its use of different mean patient weights. Using the ERG's preferred log-normal approach to modelling survival (section 3.10) predicted shorter overall survival for patients in both arms, so that olaratumab plus doxorubicin was associated with a smaller survival benefit than was modelled in the company's base case. Modelling survival using the log-normal approach increased the ICER by £8,000 per QALY gained. Assuming day-case administration of olaratumab plus doxorubicin (section 3.12) increased the ICER by £3,000 per QALY gained. Assuming a mean patient weight of 82.5 kg (section 3.13) increased the ICER by £2,000 per QALY gained. Taken together, these assumptions produced an ICER for olaratumab plus doxorubicin compared with doxorubicin alone of around £60,000 per QALY. The committee accepted that the mean patient weight used by the company was reasonable, but agreed with the ERG in its use of a log-normal approach to modelling overall survival and the higher administration costs than those presented by the company.

Cost effectiveness

The most plausible ICER for the overall population is likely to be closer to £60,000 than the company's estimate of £46,000

3.15 The committee considered the company's base-case ICER of £46,076 per QALY gained, and acknowledged that the main driver of this estimate was the extrapolation of overall survival based on immature trial data. It heard from the clinical experts that the company's estimates of overall survival, for both doxorubicin alone and combination therapy, are likely to be over-

optimistic and those from the ERG are more plausible. The committee agreed that how overall survival was extrapolated could have a large effect on the ICER, but whichever method was used the data were immature and any estimate of overall survival was highly uncertain. It preferred the ERG's use of log-normal modelling with the assumption of day-case treatment, because the log-normal model resulted in more clinically plausible estimates of overall survival (section 3.14). This produced an ICER closer to £60,000 per QALY gained, which is outside the range usually considered to be a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). Based on the current evidence, the committee concluded that it could not recommend olaratumab plus doxorubicin for untreated, advanced soft tissue sarcoma for routine use in the NHS.

End of life

Olaratumab meets the end-of-life criteria

3.16 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's [Cancer Drugs Fund technology appraisal process and methods](#). It noted that there were varying estimates of life expectancy with doxorubicin alone (the current standard of care). In the JGDG trial, median overall survival in the doxorubicin arm for the intention-to-treat population was 14.7 months. The company's model predicted mean overall survival with doxorubicin of 2.32 years and the ERG estimated it to be 1.83 years for the first-line population. The committee noted the immaturity of the survival data in the trial (section 3.6) and recalled its previous conclusion that the company's model overestimated life expectancy in both arms. However, based on both the overall survival in the control arm of the trial and the ERG's log-normal extrapolation of overall survival, the committee considered that olaratumab plus doxorubicin met the short life-expectancy criterion. It also noted that 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.

Cancer Drugs Fund

3.17 Having concluded that it could not make a recommendation for routine use, the committee considered if it could recommend olaratumab plus doxorubicin for use in the Cancer Drugs Fund. It discussed the new arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting the [addendum to the NICE process and methods guides](#). Under the new arrangements, drugs that appear promising, but for which the evidence is not robust enough for routine use, may be given a conditional recommendation by NICE and made available to NHS patients through the Cancer Drugs Fund. The committee was aware that in considering this, the following criteria must be met:

- the ICERs have the plausible potential to satisfy the criteria for routine use
- it is possible that the clinical uncertainty can be addressed through collection of outcome data and inform a subsequent update of the guidance.

Olaratumab is recommended for use within the Cancer Drugs Fund

3.18 The committee was aware that the company expressed an interest in olaratumab being considered for funding through the Cancer Drugs Fund. The committee recalled that any recommendations it made should consider olaratumab plus doxorubicin for untreated, advanced soft tissue sarcoma. It considered that the ICER for olaratumab plus doxorubicin was very uncertain, and could be anywhere between £46,000 (company base case) and £60,000 (ERG base case) per QALY gained (section 3.14) and is likely to be closer to £60,000 per QALY (section 3.15). However, it acknowledged that olaratumab has the plausible potential to satisfy the criteria for routine use, taking into account its conclusion on the end-of-life criteria (section 3.16). The committee highlighted that JGDG showed

unprecedented benefits in overall survival. The committee was aware that although there were uncertainties in the clinical-effectiveness evidence in terms of the immature overall survival data, and the difference between progression-free survival and overall survival benefit, further data is anticipated to be available in December 2020 from the ANNOUNCE trial. This data would help to address these uncertainties and allow for a better informed cost-effectiveness estimate. The committee also acknowledged that data collected from use in the NHS through the Cancer Drugs Fund via the Systemic Anti-Cancer Therapy dataset would offer further supportive evidence for olaratumab. The committee understood that NICE, NHS England and the company would undertake further discussions to formalise the managed access agreement before the publication of guidance. The committee therefore concluded that olaratumab plus doxorubicin met the criteria for inclusion in the Cancer Drugs Fund and recommended it as an option for use in the Cancer Drugs Fund for untreated, advanced soft tissue sarcoma if the conditions in the managed access agreement are followed.

4 Implementation

- 4.1 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a patient has advanced soft tissue sarcoma and the doctor responsible for their care thinks that olaratumab is the right treatment, it should be available for use, in line with NICE's recommendations and the Cancer Drugs Fund criteria in the managed access agreement. Further information can be found in NHS England's [Appraisal and funding of cancer drugs from July 2016 \(including the new Cancer Drugs Fund\) – A new deal for patients, taxpayers and industry](#).
- 4.2 Olaratumab has been recommended according to the conditions in the managed access agreement. As part of this, NHS England and Eli Lilly have a commercial access agreement that makes olaratumab available to

the NHS at a reduced cost. The financial terms of the agreement are commercial in confidence. Any enquiries from NHS organisations about the commercial access agreement should be directed to [NICE to add details at time of publication]

5 Recommendations for data collection

- 5.1 As a condition of the positive recommendation and the managed access arrangement, the company is required to collect efficacy data from the ANNOUNCE trial. Data on treatment duration and survival will also be collected via the Systemic Anti-Cancer Therapy data set.

6 Review of guidance

- 6.1 This guidance will be updated when the data collection period has ended. This is anticipated to be December 2020, when the results of the ANNOUNCE trial are expected to be available. The process for exiting the Cancer Drugs Fund will begin at this point and the review of the NICE guidance will start.
- 6.2 As part of the managed access agreement, the technology will continue to be available via the Cancer Drugs Fund after the data collection period has ended and while the guidance is being reviewed. This assumes that the data collection period ends as planned and the review of guidance follows the standard timelines described in the [addendum](#) to NICE's methods and processes when appraising cancer technologies.

Dr Jane Adam
Chair, appraisal committee
June 2017

7 Appraisal committee members and NICE project team

Appraisal committee members

The technology appraisal committees are standing advisory committees of NICE. This topic was considered by members of the existing standing committees who have met to reconsider drugs funded by the Cancer Drugs Fund. The names of the members who attended are in the [minutes](#) of the appraisal committee meeting, which are posted on the NICE website.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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