

**ANNEX I**  
**SUMMARY OF PRODUCT CHARACTERISTICS**

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## **1. NAME OF THE MEDICINAL PRODUCT**

Lartruvo 10 mg/mL concentrate for solution for infusion

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

One mL of concentrate for solution for infusion contains 10 mg of olaratumab.

Each 19 mL vial contains 190 mg of olaratumab.

Each 50 mL vial contains 500 mg of olaratumab.

Olaratumab is a human IgG1 monoclonal antibody produced in murine (NS0) cells by recombinant DNA technology.

### Excipient with known effect

Each 19mL vial contains approximately 22 mg (1 mmol) sodium.

Each 50 mL vial contains approximately 57 mg (2.5 mmol) sodium.

For the full list of excipients, see section 6.1.

## **3. PHARMACEUTICAL FORM**

Concentrate for solution for infusion (sterile concentrate).

The concentrate is clear to slightly opalescent and colourless to slightly yellow solution without visible particles.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

Lartruvo is indicated in combination with doxorubicin 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 (see section 5.1).

### **4.2 Posology and method of administration**

Olaratumab therapy must be initiated and supervised by physicians experienced in oncology. Patients should be monitored during the infusion for signs and symptoms of infusion-related reactions (IRRs) in a setting with available resuscitation equipment (see section 4.4).

#### Posology

The recommended dose of olaratumab is 15 mg/kg administered by intravenous infusion on days 1 and 8 of each 3 week cycle until disease progression or unacceptable toxicity. Lartruvo is administered in combination with doxorubicin for up to 8 cycles of treatment, followed by Lartruvo monotherapy in

patients whose disease has not progressed. Doxorubicin is given on day 1 of each cycle following the Lartruvo infusion.

*Premedication*

Premedication with an H1 antagonist (e.g., diphenhydramine) and dexamethasone (or equivalent medicinal products) should be given, intravenously, 30–60 minutes prior to the olaratumab doses on days 1 and 8 of cycle 1 in all patients. For subsequent cycles, premedication with an H1 antagonist (e.g., diphenhydramine) should be given intravenously 30–60 minutes prior to each dose of olaratumab.

For patients who experience Grade 1 or 2 IRR, the infusion should be interrupted and paracetamol, H1 antagonist and dexamethasone (or equivalent medicinal products) administered as needed. For all subsequent infusions, premedication with the following (or equivalent medicinal products) diphenhydramine hydrochloride (intravenously), paracetamol, and dexamethasone, should be given.

In the event that intravenous administration of an H1 antagonist is not possible, equivalent alternative premedication should be given (e.g. oral diphenhydramine hydrochloride at least 90 minutes prior to the infusion).

Posology adjustments for olaratumab

For dose adjustment recommendations related to doxorubicin, refer to the current doxorubicin prescribing information.

*Infusion-related reactions (IRRs)*

Recommendations for the management of olaratumab IRRs are provided in table 1.

**Table 1 – Management recommendations for infusion-related reactions (IRRs)**

Toxicity grade <sup>a</sup>	Management recommendations (any occurrence)
Grade 1-2	<ul style="list-style-type: none"> <li>• Stop the infusion</li> <li>• Paracetamol, H1 antagonist and dexamethasone should be administered as needed (see premedication section)</li> <li>• Once the reaction has resolved, resume infusion at a 50 % decreased infusion rate.<sup>b</sup></li> <li>• Monitor patient for worsening of condition.</li> <li>• For subsequent infusions, please see premedication section.</li> </ul>
Grade 3-4	<ul style="list-style-type: none"> <li>• Immediately and permanently discontinue treatment with olaratumab (see section 4.4).</li> </ul>

<sup>a</sup> Grade per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03

<sup>b</sup> Once the infusion rate has been reduced for a Grade 1 or 2 infusion-related reaction, it is recommended that the lower infusion rate be utilized for all subsequent infusions. The infusion duration should not exceed 2 hours.

*Other non-haematology toxicities*

For serious Grade  $\geq 3$  non-haematologic toxicity deemed related to olaratumab, the dose of olaratumab should be withheld until toxicity is  $\leq$  Grade 1 or has returned to pretreatment baseline. For subsequent infusions, the dose should be reduced to 12 mg/kg for serious Grade 3 toxicities and to 10 mg/kg for Grade 4 toxicities. If a Grade 3 toxicity recurs despite the dose reduction, the dose should be reduced further to 10 mg/kg. In case of recurrence of a Grade 4 toxicity, treatment with olaratumab should be permanently discontinued.

*Neutropenia*

If neutropenic fever/infection or Grade 4 neutropenia lasting longer than 1 week occurs, administration of olaratumab should be temporarily discontinued until the absolute neutrophil count is 1,000 /  $\mu\text{L}$  or higher and then the dose of olaratumab should be resumed at the reduced dose of 12 mg/kg. If neutropenic fever/infection or Grade 4 neutropenia lasting longer than 1 week recurs despite dose reduction, the dose should be reduced further to 10 mg/kg.

### Special populations

#### *Elderly (> 65 years)*

Data on very elderly patients (> 75 years) are very limited (see sections 4.8 and 5.1). No dose reductions other than those recommended for the general patient population are necessary.

#### *Renal impairment*

There have been no formal studies with olaratumab in patients with renal impairment. PopPK data suggest that no dose adjustments are required in patients with mild or moderate renal impairment. There are no data regarding olaratumab administration in patients with severe renal impairment (calculated creatinine clearance < 30 mL/min) (see section 5.2).

#### *Hepatic impairment*

There have been no formal studies with olaratumab in patients with hepatic impairment. PopPK data suggest that no dose adjustments are required in patients with mild hepatic impairment. There are very limited data regarding olaratumab administration in patients with moderate hepatic impairment. There are no data in patients with severe hepatic impairment (see section 5.2).

#### *Paediatric population*

The safety and efficacy of olaratumab in children aged 0 to 18 years of age have not yet been established. No data are available.

### Method of administration

After dilution in sodium chloride 9 mg/mL (0.9 %) solution for injection, olaratumab is administered as an intravenous infusion over approximately 60 minutes. In order to accommodate larger infusion volumes that may be needed for patients requiring higher doses, the duration of infusion should be increased such that the maximum infusion rate of 25 mg/minute is not exceeded.

For instructions on dilution of the medicinal product before administration, see section 6.6.

## **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

## **4.4 Special warnings and precautions for use**

### Infusion-related reactions

Infusion-related reactions (IRRs), including anaphylactic reactions, were reported in clinical trials with olaratumab. The majority of these reactions occurred during or following the first olaratumab infusion. Symptoms of IRRs included flushing, shortness of breath, bronchospasm, or fever/chills, and in some cases manifested as severe hypotension, anaphylactic shock, or fatal cardiac arrest. Severe IRRs such as anaphylactic reactions can occur despite the use of premedication. Patients should be monitored during the infusion for signs and symptoms of IRRs in a setting with available resuscitation equipment. For management and dose adjustments in patients who experience Grade 1 or 2 IRR during the infusion, see section 4.2. In patients who have experienced a previous Grade 1 or 2 IRR, premedication with diphenhydramine hydrochloride (intravenously), paracetamol, and dexamethasone is recommended. Olaratumab should be immediately and permanently discontinued in patients who experience Grade 3 or 4 IRR (see sections 4.2 and 4.8).

### Neutropenia

Patients receiving olaratumab and doxorubicin are at risk of neutropenia (see section 4.8). Neutrophil count should be checked prior to Olaratumab dosing on Day 1 and Day 8 of each cycle. Neutrophil count should be monitored during the treatment with olaratumab and doxorubicin and supportive care should be administered such as antibiotics or G-CSF as per local guidelines. For dosage adjustments related to neutropenia, refer to section 4.2.

### Haemorrhagic events

Patients receiving olaratumab and doxorubicin are at risk of haemorrhagic events (see section 4.8). Platelet counts should be checked prior to olaratumab dosing on Day 1 and Day 8 of each cycle. Coagulation parameters should be monitored in patients with conditions predisposing to bleeding, such as anticoagulant use. In a study of olaratumab in combination with liposomal doxorubicin, there was one case of fatal intracranial haemorrhage in a patient who had experienced a fall while on treatment.

### Anthracycline pre-treated patients

The risk of cardiac toxicity rises with increasing cumulative doses of anthracyclines, including doxorubicin. There are no data for the combination of olaratumab and doxorubicin in anthracycline pre-treated patients, including pre-treatment with doxorubicin (see section 4.1).

### Sodium restricted diet

This medicinal product contains 22 mg sodium per each 19 mL vial and 57 mg sodium per each 50 mL vial. To be taken into consideration by patients on a controlled sodium diet.

### Cardiac toxicity

Doxorubicin can cause cardiotoxicity. The risk of toxicity rises with increasing cumulative doses and is higher in individuals with a history of cardiomyopathy, mediastinal irradiation or pre-existing cardiac disease. To minimise doxorubicin-related cardiotoxicity, the use of appropriate cardio-protective measures (LVEF measurement, such as ECHO or MUGA scan, ECG monitoring, and/or use of cardioprotective agents) should be considered and planned in all patients before the start and throughout the treatment.

Please refer to doxorubicin SmPC for recommendation on cardiac monitoring.

In the phase 2 trial, patients in both treatment groups that received 5 or more cycles of doxorubicin received dexrazoxane prior to each dose of doxorubicin from cycle 5 onwards to minimize the risk of doxorubicin-related cardiotoxicity (see sections 4.8 and 5.1).

### Hepatic impairment

As doxorubicin is rapidly metabolised and predominantly eliminated by the biliary system, the toxicity of doxorubicin is enhanced in patients with hepatic impairment. Refer to doxorubicin SmPC for appropriate monitoring of hepatic function and doxorubicin dose adjustments in patients with impaired liver function.

## **4.5 Interaction with other medicinal products and other forms of interaction**

Olaratumab is a human monoclonal antibody. In a dedicated DDI study, no pharmacokinetic interactions were observed in patients between olaratumab and doxorubicin.

No other formal DDI studies with olaratumab and medicinal products commonly used in cancer patients, including those with STS (e.g. antiemetics, analgesics, anti-diarrheal drugs, oral contraceptives, etc.), have been performed.

As monoclonal antibodies are not metabolised by cytochrome P450 (CYP) enzymes or other drug metabolising enzymes, inhibition or induction of these enzymes by co-administered medicinal

products is not anticipated to affect the pharmacokinetics of olaratumab. Conversely, olaratumab is not anticipated to affect the pharmacokinetics of co-administered medicinal products.

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including doxorubicin may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving olaratumab in combination with doxorubicin.

#### **4.6 Fertility, pregnancy and lactation**

##### Women of childbearing potential/contraception in females

Women of childbearing potential should be advised to avoid becoming pregnant while on olaratumab and should be informed of the potential hazard to the pregnancy and foetus. Women of childbearing potential should be advised to use effective contraception during treatment and for at least 3 months following the last dose of olaratumab.

##### Pregnancy

There are no or limited amount of data from the use of olaratumab in pregnant women. Reproductive and development toxicity study conducted with an anti-murine PDGFR $\alpha$  antibody in mice showed foetal malformations and skeletal alterations (see section 5.3).

Based on its mechanism of action (see section 5.1), olaratumab has the potential to cause foetal harm. Olaratumab is not recommended during pregnancy and in women of childbearing potential not using contraception, unless the potential benefit justifies the potential risk to the foetus.

##### Breast-feeding

It is not known whether olaratumab is excreted in human milk. Human IgG is excreted in human milk, therefore breast-feeding is not recommended during treatment with olaratumab and for at least 3 months following the last dose.

##### Fertility

There are no data on the effect of olaratumab on human fertility.

#### **4.7 Effects on ability to drive and use machines**

Olaratumab may have minor influence on the ability to drive and use machines. Due to frequent occurrence of fatigue, patients should be advised to use caution when driving or operating machinery.

#### **4.8 Undesirable effects**

##### Summary of the safety profile

##### *Olaratumab-treated patients from Phase 2 study*

In the olaratumab plus doxorubicin arm, the most serious (Grade  $\geq 3$ ) adverse drug reactions (ADRs) observed were neutropenia (54.7 %) and musculoskeletal pain (7.8 %).

The most frequently occurring ADRs were nausea, musculoskeletal pain, neutropenia and mucositis.

The most frequent ADRs associated with permanent treatment discontinuation occurred in 3 (4.7 %) patients of which the most frequent were infusion-related reactions (3.1 %) and mucositis (1.6 %).

Known toxicities reported for doxorubicin, observed in the combination of olaratumab and doxorubicin include fatigue, anaemia, thrombocytopenia and alopecia. Please refer to the doxorubicin SmPC for complete descriptions of all adverse events associated with doxorubicin treatment

### Tabulated list of adverse reactions

ADRs which were reported in patients with soft tissue sarcoma treated with olaratumab in combination with doxorubicin in the Phase 2 study are listed below in Table 2 in MedDRA body system organ class, frequency and grade of severity. The following convention has been used for classification of frequency:

Very common ( $\geq 1/10$ )

Common ( $\geq 1/100$  to  $< 1/10$ )

Uncommon ( $\geq 1/1,000$  to  $< 1/100$ )

Rare ( $\geq 1/10,000$  to  $< 1/1,000$ )

Very rare ( $< 1/10,000$ )

Within each frequency grouping, ADRs are presented in order of decreasing seriousness.

**Table 2: Adverse reactions in patients receiving olaratumab plus doxorubicin for soft tissue sarcoma during the Phase 2 portion of a Phase 1b/2 study**

<b>System organ class</b>	<b>Adverse Reaction<sup>a</sup></b>	<b>Frequency overall</b>	<b>Grade 3/4 frequency</b>
<b>Blood and lymphatic system disorders</b>	Neutropenia	Very Common	Very Common
	Lymphopenia	Very Common	Common
<b>Nervous system disorders</b>	Headache	Very Common	None reported
<b>Gastrointestinal disorders</b>	Diarrhoea	Very Common	Common
	Mucositis	Very Common	Common
	Nausea	Very Common	Common
	Vomiting	Very Common	None reported
<b>Musculoskeletal and connective tissue disorders</b>	Musculoskeletal Pain <sup>b</sup>	Very Common	Common
<b>General disorders and administrative site conditions</b>	Infusion-related Reactions <sup>c</sup>	Very Common	Common

<sup>a</sup> Refer to NCI CTCAE Criteria (Version 4.03) for each Grade of toxicity

<sup>b</sup> Musculoskeletal pain includes arthralgia, back pain, bone pain, flank pain, groin pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, muscle spasms, neck pain, and pain in extremity.

<sup>c</sup> Infusion-related reactions includes anaphylactic reactions/anaphylactic shock.

### Description of selected ADRs

#### *Infusion-related reactions (IRRs)*

IRRs were reported in 12.5 % of patients and mainly present as chills, fever or dyspnoea. Severe IRRs, also including a fatal case (see section 4.4) were reported in 3.1 % of patients and mainly presented with shortness of breath, loss of consciousness and hypotension. All severe IRRs occurred during or immediately after the first administration of olaratumab.

#### *Neutropenia*

In the phase 2 trial, the incidence of neutropenia was 59.4 % (all Grades) and 54.7 % (Grade 3) in the olaratumab plus doxorubicin arm and 38.5 % (all Grades) and 33.8 % (Grade 3) in the doxorubicin alone arm. The rate of febrile neutropenia was 12.5 % in the olaratumab plus doxorubicin arm and 13.8 % in the doxorubicin alone arm. For dose adjustments, refer to section 4.2

#### *Musculoskeletal pain*

In the phase 2 trial the incidence of Musculoskeletal pain was 64.1 % (all Grades) and 7.8 % (Grade 3) in the olaratumab plus doxorubicin arm and 24.6 % (all Grades) and 1.5 % (Grade 3) in the

doxorubicin alone arm. In the majority of patients the pain was related to the patients' underlying cancer or metastases or pre-existing or concomitant conditions. The majority of these events occurred in the first 4 cycles. The pain can last from few days to up to 200 days. In some patients there was a recurrence of pain. The pain did not worsen with time or during recurrence.

#### *Cardiac toxicity*

No clinically meaningful difference in doxorubicin-related cardiotoxicity was observed between the two treatment arms of the study. The rate of cardiac arrhythmias was similar in both arms (15.6 % in the Investigational Arm and 15.4 % in the Control Arm). The rate of treatment-emergent cardiac dysfunction was comparable between the two treatment arms (7.8 % in the Investigational Arm and 6.2 % in the Control Arm).

#### *Haemorrhagic events*

In the phase 2 trial, the frequency of haemorrhagic events considered related to any study drug was 3.1 % in either treatment arm. All of these events were Grade 1/2 and were confounded by multiple factors. Three Grade  $\geq 3$  events, including one fatal, have been reported across the clinical development programme of olaratumab (see section 4.4).

#### *Toxicity in the elderly*

There was a higher incidence of Grade  $\geq 3$  adverse reactions, adverse reactions leading to discontinuation and a higher rate of haematological toxicity in the elderly population compared to the overall study population (see section 4.2). The rates of discontinuation were comparable between treatment arms across all age groups.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in [Appendix V](#).

## **4.9 Overdose**

There is no experience with Lartruvo overdose in human clinical trials. Lartruvo has been administered in a Phase 1 study up to 20 mg/kg on days 1 and 8 of a 21 day cycle without reaching a maximum tolerated dose. In case of overdose, use supportive therapy. There is no known antidote to Lartruvo overdose.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC27

#### Mechanism of action

Olaratumab is an antagonist of platelet derived growth factor receptor- $\alpha$  (PDGFR- $\alpha$ ), expressed on tumour and stromal cells. Olaratumab is a targeted, recombinant, fully human immunoglobulin G subclass 1 (IgG1) monoclonal antibody that specifically binds PDGFR- $\alpha$ , blocking PDGF AA, -BB, and -CC binding and receptor activation. As a result, *in vitro* olaratumab inhibits PDGFR- $\alpha$  pathway signalling in tumour and stromal cells. In addition, *in vivo* olaratumab has been shown to disrupt the PDGFR- $\alpha$  pathway in tumour cells and inhibit tumour growth.

#### Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity.

Overall, a low incidence of both treatment emergent anti-drug antibodies and neutralising antibodies were detected in clinical trial samples.

### Clinical efficacy and safety

The efficacy and safety of olaratumab was assessed in a Phase 1b/2, multi-centre study in anthracycline naïve patients with histologically or cytologically confirmed, advanced soft tissue sarcoma not amenable to receive surgery or radiotherapy with curative intent. Patients with gastrointestinal stromal tumours (GIST) or Kaposi sarcoma were not enrolled. The Phase 2 portion of the study was a randomised, open label study of olaratumab plus doxorubicin versus doxorubicin alone. A total of 133 patients were randomised, of whom 129 received at least one dose of study treatment (64 in the olaratumab plus doxorubicin arm and 65 in the doxorubicin arm). Patients were required to have histologically or cytologically confirmed, advanced soft tissue sarcoma and ECOG performance status of 0-2. Randomisation was stratified by PDGFR- $\alpha$  expression (positive versus negative), number of previous lines of treatment (0 versus 1 or more lines), histological tumour type (leiomyosarcoma, synovial sarcoma, and others) and ECOG performance status (0 or 1 versus 2).

Patients were randomised in a 1:1 ratio to either olaratumab (15 mg/kg) on Day 1 and Day 8 plus doxorubicin (75 mg/m<sup>2</sup>) on Day 1 of each 21-day cycle for up to 8 cycles or doxorubicin (75 mg/m<sup>2</sup>) alone on Day 1 of each 21-day cycle, also for up to 8 cycles. Olaratumab and doxorubicin were administered by intravenous infusion. During Cycles 5 to 8 on both arms, dexrazoxane (dosed at a ratio of 10:1 to the administered dose of doxorubicin) could be administered on Day 1 of each cycle at the investigator's discretion to reduce potential doxorubicin-related cardiotoxicity. All patients receiving more than 4 cycles of doxorubicin received dexrazoxane. Patients in the olaratumab plus doxorubicin arm could continue on olaratumab monotherapy until disease progression, unacceptable toxicity or any other reason for treatment discontinuation occurred.

Demographics and baseline characteristics were quite similar between treatment arms in the phase 2 portion of the clinical trial. The median age was 58 years with 42 patients  $\geq$  65 years of age. 86.4 % of the patients were Caucasian. More than 25 different soft tissue sarcoma subtypes were represented in this trial, the most frequent being leiomyosarcoma (38.4 %), undifferentiated pleomorphic sarcoma (18.1 %) and liposarcoma (17.3 %). Other subtypes were infrequently represented. Patients had received 0-4 previous lines of therapy for treatment of advanced disease but had not previously received treatment with anthracyclines. The number of patients receiving post-study systemic therapy was similar between arms. Ten patients in the olaratumab plus doxorubicin arm and 5 patients in the doxorubicin arm received post-study radiotherapy only. 3 patients in the olaratumab plus doxorubicin arm and 1 patient in the doxorubicin arm had post-study surgery only. 2 patients in the olaratumab plus doxorubicin arm and none in the doxorubicin arm received both post-study radiotherapy and surgery.

The median cumulative dose of doxorubicin was 487.6 mg/m<sup>2</sup> in the olaratumab plus doxorubicin arm and 299.6 mg/m<sup>2</sup> in the doxorubicin alone arm. The primary efficacy outcome measure was progression free survival (PFS) by investigator assessment. Key secondary efficacy outcome measures were overall survival (OS) and objective response rate (ORR) (see Table 3). The study met its primary endpoint (PFS). PFS according to a post-hoc, blinded, independent assessment was 8.2 months vs 4.4 months; HR = 0.670; p = 0.1208. A statistically significant improvement in OS was seen in the olaratumab plus doxorubicin arm in comparison to treatment with doxorubicin alone in the overall population. The main analysis was performed in the following two subgroups: Leiomyosarcoma (LMS) and non-LMS (other). Subgroups analysis of OS is shown in figure 2. Difference in objective response rate [complete response (CR) + partial response (PR)] according to investigator assessment was not statistically significant (18.2 % vs 11.9 % in patients randomised to olaratumab plus doxorubicin compared to patients randomized to doxorubicin respectively).

Efficacy results are shown in Table 3 and Figures 1 and 2.

**Table 3. Summary of survival data – ITT population**

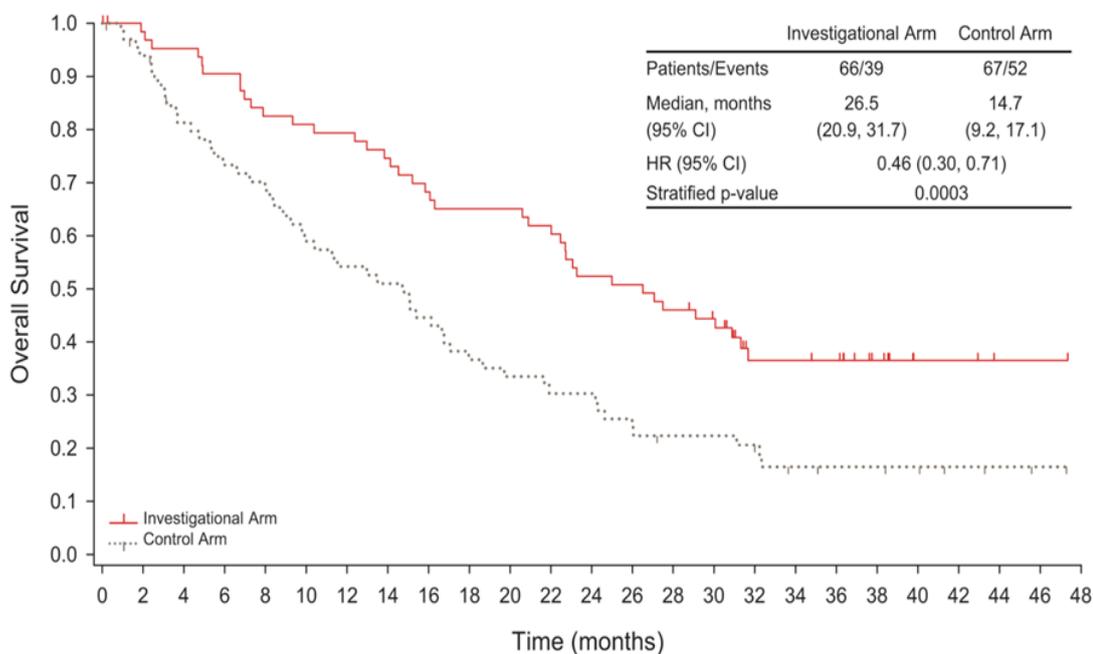
	<b>Lartruvo plus doxorubicin (n = 66)</b>	<b>Doxorubicin alone (n = 67)</b>
<b>Progression free survival, months*</b>		
Median (95 % CI)	6.6 (4.1, 8.3)	4.1 (2.8, 5.4)
Hazard ratio (95 % CI)	0.672 (0.442, 1.021)	
p-value	0.0615**	
<b>Overall survival, months</b>		
Median (95 % CI)	26.5 (20.9, 31.7)	14.7 (9.2, 17.1)
Hazard ratio (95 % CI)	0.463 (0.301, 0.710)	
p-value	0.0003	

Abbreviations: CI = confidence interval

\* By investigator assessment

\*\*Met phase 2 protocol defined significance level of 0.19

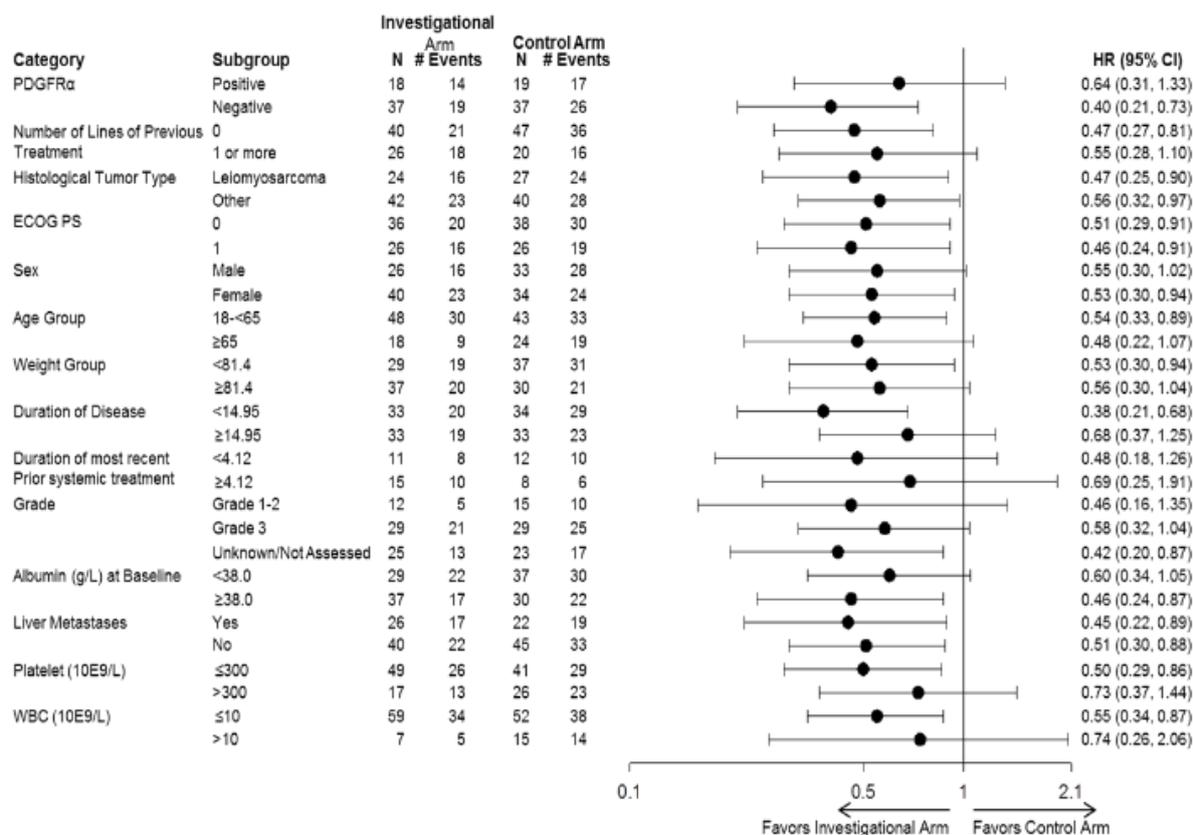
**Figure 1. Kaplan-Meier curves of overall survival for Lartruvo plus doxorubicin versus doxorubicin alone**



**Number at Risk**

Investigational Arm	66	62	60	57	52	51	50	47	43	41	41	39	33	32	29	26	16	16	15	8	3	3	1	1	0
Control Arm	67	61	51	46	43	37	34	32	28	23	21	19	19	15	13	13	10	7	6	6	5	3	2	1	0

**Figure 2. Forest plot for subgroup analysis of overall survival (ITT population)**



Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with olaratumab in one or more subsets of the paediatric population in soft tissue sarcoma (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called ‘conditional approval’ scheme.

This means that further evidence on this medicinal product is awaited.

The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary .

**5.2 Pharmacokinetic properties**

Absorption

Olaratumab is administered as an intravenous infusion only.

Distribution

The population pharmacokinetic (PopPK) model-based mean (CV %) volume of distribution of olaratumab at steady state (V<sub>ss</sub>) was 7.7 L (16 %).

Elimination

The PopPK model-based mean (CV %) clearance for olaratumab was 0.56 L/day (33 %). This corresponds to a mean terminal half-life of approximately 11 days.

Special populations

Age, sex, and race had no clinically meaningful effect on the PK of olaratumab based on a PopPK analysis. Clearance and volume of distribution had a positive correlation with body weight.

### *Renal impairment*

No formal studies have been conducted to evaluate the effect of renal impairment on the PK of olaratumab. Based on a PopPK analysis, no clinically meaningful differences in the clearance of olaratumab were observed in patients with mild (calculated creatinine clearance [CLcr] 60-89 mL/min, n = 43), or moderate (CLcr 30-59 mL/min, n = 15) renal impairment compared to patients with normal renal function (CLcr  $\geq$ 90 mL/min, n = 85). No data were available from patients with severe renal impairment (CLcr 15-29 mL/min).

### *Hepatic impairment*

No formal studies have been conducted to evaluate the effect of hepatic impairment on the PK of olaratumab. Based on a PopPK analysis, no clinically meaningful differences in the clearance of olaratumab were observed in patients with mild (total bilirubin within upper limit of normal [ULN] and AST > ULN, or total bilirubin > 1.0-1.5 times ULN and any AST level, n = 16), or moderate (total bilirubin > 1.5-3.0 times ULN, n = 1) hepatic impairment compared to patients with normal hepatic function (total bilirubin and AST  $\leq$  ULN, n = 126). No data were available from patients with severe hepatic impairment (total bilirubin > 3.0 times ULN and any AST level).

## **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on repeat dose toxicity studies in monkeys.

No animal studies have been performed to test olaratumab for potential of carcinogenicity, genotoxicity, or fertility impairment. Administration of an anti-murine PDGFR- $\alpha$  surrogate antibody to pregnant mice during organogenesis at 50 and 150 mg/kg resulted in increased malformations (abnormal eyelid development) and skeletal alterations (frontal/parietal additional ossification site). The foetal effects in mice administered the surrogate antibody occurred at exposures less than the AUC exposure at the maximum recommended human dose of 15 mg/kg olaratumab.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

Mannitol (E421)  
Glycine (E640)  
Sodium chloride  
L-Histidine monohydrochloride monohydrate  
L-Histidine  
Polysorbate 20 (E432)  
Water for injections

### **6.2 Incompatibilities**

The medicinal product should not be administered or mixed with dextrose containing solutions.

### **6.3 Shelf life**

#### Unopened vial

2 years.

#### After dilution

This product is preservative free. From a microbiological point of view the prepared dosing solution should be used immediately. If not used immediately, the dosing solution should be stored under refrigeration for up to 24 hours at 2 °C to 8 °C and up to an additional 8 hours at room temperature (up

to 25 °C) assuming dilution has taken place in controlled and validated aseptic conditions. Storage times include the duration of infusion.

#### **6.4 Special precautions for storage**

Store in a refrigerator (2° C - 8° C).

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

#### **6.5 Nature and contents of container**

19 mL solution in a vial (Type I glass) with a chlorobutyl elastomeric stopper, an aluminium seal and a polypropylene cap.

50 mL solution in a vial (Type I glass) with a chlorobutyl elastomeric stopper, an aluminium seal and a polypropylene cap.

Pack of 1 vial of 19 mL.

Pack of 2 vials of 19 mL.

Pack of 1 vial of 50 mL.

Not all pack sizes may be marketed.

#### **6.6 Special precautions for disposal and other handling**

The infusion solution should be prepared using aseptic technique to ensure the sterility of the prepared solution.

Each vial is intended for single use only. Do not shake the vial. The content of the vials should be inspected for particulate matter and discolouration (the concentrate for solution for infusion should be clear to slightly opalescent and colourless to slightly yellow without visible particles) prior to administration. If particulate matter or discolouration is identified, the vial must be discarded. The dose and volume of olaratumab needed should be calculated to prepare the infusion solution. Vials contain 190 mg or 500 mg as a 10 mg/mL solution of olaratumab. Only use sodium chloride 9 mg/mL (0.9 %) solution for injection as a diluent.

##### In case of prefilled intravenous infusion container usage

Based on the calculated volume of olaratumab, the corresponding volume of sodium chloride 9 mg/mL (0.9 %) solution for injection should be removed from the prefilled 250 mL intravenous container. The calculated volume of olaratumab should be aseptically transferred to the intravenous container. The final total volume in the container should be 250 mL. The container should be gently inverted to ensure adequate mixing. **DO NOT FREEZE OR SHAKE** the infusion solution.

##### In case of empty intravenous infusion container usage

The calculated volume of olaratumab should be aseptically transferred into an empty intravenous infusion container. A sufficient quantity of sodium chloride 9 mg/mL (0.9 %) solution for injection should be added to the container to make the total volume 250 mL. The container should be gently inverted to ensure adequate mixing. **DO NOT FREEZE OR SHAKE** the infusion solution.

Administer via an infusion pump. A separate infusion line must be used and the line must be flushed with sodium chloride 9 mg/mL (0.9 %) solution for injection at the end of the infusion.

Any unused portion of olaratumab left in a vial should be discarded, as the product contains no antimicrobial preservatives.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**7. MARKETING AUTHORISATION HOLDER**

Eli Lilly Nederland B.V.  
Papendorpseweg 83  
3528 BJ Utrecht  
The Netherlands

**8. MARKETING AUTHORISATION NUMBER(S)**

EU/1/16/1143/001-003

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 9 November 2016  
Date of latest renewal: 21 September 2017

**10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

## **ANNEX II**

- A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**
- E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION**

**A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer(s) of the biological active substance(s)

ImClone Systems LLC  
33 ImClone Drive  
Branchburg  
New Jersey  
NJ 08876  
UNITED STATES

Name and address of the manufacturer(s) responsible for batch release

Lilly S.A.  
Avda. de la Industria 30  
Alcobendas  
28108 Madrid  
SPAIN

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

• **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal. The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

• **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

• **Additional risk minimisation measures**

Not applicable.

**E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION**

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

<b>Description</b>	<b>Due date</b>
In order to further confirm the efficacy and safety of olaratumab in the treatment of patients with advanced soft tissue sarcoma, the MAH should submit the clinical study report of the phase III study JGDJ comparing doxorubicin plus olaratumab versus doxorubicin in patients with advanced or metastatic STS (including exploratory biomarker data).	31 January 2020

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

## **A. LABELLING**

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON – 50 mL vial**

**1. NAME OF THE MEDICINAL PRODUCT**

Lartruvo 10 mg/mL concentrate for solution for infusion  
olaratumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One mL of concentrate contains 10 mg of olaratumab.  
One vial of 50 mL contains 500 mg olaratumab.

**3. LIST OF EXCIPIENTS**

Excipients: mannitol, glycine, sodium chloride, L-histidine monohydrochloride monohydrate, L-histidine, polysorbate 20 and water for injections. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Concentrate for solution for infusion

500 mg/50 mL  
1 vial

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
For intravenous use after dilution.  
For single use only.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

Do not shake.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator.  
Do not freeze.  
Keep the vial in the outer carton in order to protect from light.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Eli Lilly Nederland B.V.  
Papendorpseweg 83,  
3528 BJ Utrecht  
The Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/16/1143/001

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:

NN:

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**CARTON – 19 mL vial**

**1. NAME OF THE MEDICINAL PRODUCT**

Lartruvo 10 mg/mL concentrate for solution for infusion  
olaratumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One mL of concentrate contains 10 mg of olaratumab.  
One vial of 19 mL contains 190 mg olaratumab.

**3. LIST OF EXCIPIENTS**

Excipients: mannitol, glycine, sodium chloride, L-histidine monohydrochloride monohydrate, L-histidine, polysorbate 20 and water for injections. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Concentrate for solution for infusion

190 mg/19 mL  
1 vial  
2 vials

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
For intravenous use after dilution.  
For single use only.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

Do not shake.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator.

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE****11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Eli Lilly Nederland B.V.

Papendorpseweg 83,

3528 BJ Utrecht

The Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/16/1143/002 – 1 vial of 19 mL.

EU/1/16/1143/003 – 2 vials of 19 mL.

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY****15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

**17. UNIQUE IDENTIFIER – 2D BARCODE**

2D barcode carrying the unique identifier included.

**18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PC:  
SN:  
NN:

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**VIAL LABEL – 50 mL vial**

**1. NAME OF THE MEDICINAL PRODUCT**

Lartruvo 10 mg/mL sterile concentrate  
olaratumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One mL of concentrate contains 10 mg of olaratumab.  
One vial of 50 mL contains 500 mg olaratumab.

**3. LIST OF EXCIPIENTS**

Excipients: mannitol, glycine, sodium chloride, L-histidine monohydrochloride monohydrate,  
L-histidine, polysorbate 20 and water for injections. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Concentrate for solution for infusion

500 mg/50 mL  
1 vial

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
For IV use after dilution.  
For single use only.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

Do not shake.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator.

Do not freeze.

Keep the vial in the outer carton.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Eli Lilly Nederland B.V.

Papendorpseweg 83,

3528 BJ Utrecht

The Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/16/1143/001

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

**PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**

**VIAL LABEL – 19 mL vial**

**1. NAME OF THE MEDICINAL PRODUCT**

Lartruvo 10 mg/mL sterile concentrate  
olaratumab

**2. STATEMENT OF ACTIVE SUBSTANCE(S)**

One mL of concentrate contains 10 mg of olaratumab.  
One vial of 19 mL contains 190 mg olaratumab.

**3. LIST OF EXCIPIENTS**

Excipients: mannitol, glycine, sodium chloride, L-histidine monohydrochloride monohydrate, L-histidine, polysorbate 20 and water for injections. See leaflet for further information.

**4. PHARMACEUTICAL FORM AND CONTENTS**

Concentrate for solution for infusion

190 mg/19 mL  
1 vial  
2 vials

**5. METHOD AND ROUTE(S) OF ADMINISTRATION**

Read the package leaflet before use.  
For IV use after dilution.  
For single use only.

**6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

**7. OTHER SPECIAL WARNING(S), IF NECESSARY**

Do not shake.

**8. EXPIRY DATE**

EXP

**9. SPECIAL STORAGE CONDITIONS**

Store in a refrigerator.

Do not freeze.

Keep the vial in the outer carton.

**10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**

**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Eli Lilly Nederland B.V.

Papendorpseweg 83,

3528 BJ Utrecht

The Netherlands

**12. MARKETING AUTHORISATION NUMBER(S)**

EU/1/16/1143/002 – 1 vial of 19 mL.

EU/1/16/1143/003 – 2 vials of 19 mL.

**13. BATCH NUMBER**

Lot

**14. GENERAL CLASSIFICATION FOR SUPPLY**

**15. INSTRUCTIONS ON USE**

**16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted.

**B. PACKAGE LEAFLET**

## Package leaflet: Information for the user

### Lartruvo 10 mg/mL concentrate for solution for infusion olaratumab

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**Read all of this leaflet carefully before you are given this medicine because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

#### What is in this leaflet

1. What Lartruvo is and what it is used for
2. What you need to know before you are given Lartruvo
3. How you are given Lartruvo
4. Possible side effects
5. How to store Lartruvo
6. Contents of the pack and other information

#### 1. What Lartruvo is and what it is used for

Lartruvo contains the active substance olaratumab, which belongs to a group of medicines called monoclonal antibodies.

Olaratumab recognises and attaches specifically to a protein known as platelet-derived growth factor receptor- $\alpha$  (PDGFR- $\alpha$ ). PDGFR- $\alpha$  is found in large amounts on some cancer cells where it stimulates the cells to grow and divide. When olaratumab attaches to PDGFR- $\alpha$  it may prevent cancer cell growth and survival.

Lartruvo is used in combination with another anti-cancer medicine called doxorubicin for the treatment of adults with advanced soft tissue sarcoma who have not been previously treated with doxorubicin. Soft tissue sarcoma is a cancer that starts in the soft tissues, such as the muscles, fat, cartilage and blood vessels.

#### 2. What you need to know before you are given Lartruvo

##### You must not be given Lartruvo

- if you are allergic to olaratumab or any of the other ingredients of this medicine (listed in section 6).

##### Warnings and precautions

You should tell your doctor about any of the following:

- if you are receiving any treatment for heart disease or liver disease

Talk to your doctor or nurse **immediately** if the following applies to you (or you are not sure):

##### – Infusion-related reaction

Infusion-related reactions may occur during treatment with Lartruvo. Such reactions may be allergic. Symptoms may include back pain, chest pain and/or tightness, chills, fever, flushing, difficulty in

breathing and wheezing. In severe cases, you may experience very low blood pressure, feel faint, and experience breathing distress caused by narrowing of the airways, which could be life-threatening. Your doctor will give you other medicines before you receive Lartruvo to reduce the risk of infusion-related reactions. Your doctor or nurse will check for side effects during and after your infusion. If you have a severe infusion-related reaction, your doctor may recommend reducing the dose of Lartruvo or stop your treatment with Lartruvo. See section 4 for more details about infusion-related reactions which may occur during or after the infusion.

– **Bleeding**

Lartruvo and doxorubicin may decrease your platelet count. Platelets help your blood to clot and a low platelet count may increase the risk of bleeding. If you experience significant bleeding, symptoms may include extreme tiredness, weakness, dizziness or changes in the colour of your stools. Your doctor will check your platelet count prior to treatment with Lartruvo.

– **Reduction in the number of white blood cells**

Lartruvo and doxorubicin may decrease the number of white blood cells (including neutrophils). White blood cells are important for fighting infection. A low white blood cell count may increase your risk for infection. Your doctor will check your white blood cell counts prior to treatment with Lartruvo.

**Children and adolescents**

Lartruvo should not be given to patients under the age of 18 years because there is no information about how it works in this age group.

**Other medicines and Lartruvo**

Tell your doctor if you are taking, have recently taken or might take any other medicines.

**Pregnancy and breast-feeding**

Before starting treatment you must tell your doctor if you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby.

Avoid getting pregnant while receiving this medicine and for at least 3 months after the last dose of Lartruvo as this medicine may harm your unborn child. Talk to your doctor about the best contraception for you.

It is not known whether olaratumab gets into breast milk and if the breast-fed infant is at risk of harm. **Ask your doctor** if you can breast-feed during or after treatment with Lartruvo.

**Driving and using machines**

It is not known if Lartruvo will affect your ability to drive. If you get any symptoms that affect your ability to concentrate and react, such as tiredness, do not drive or use machines until the effect goes away.

**Lartruvo contains sodium**

This medicine contains 22 mg sodium in each 19 mL vial and 57 mg sodium in each 50 mL vial. This should be taken into consideration if you are on a controlled sodium diet.

**3. How you are given Lartruvo**

A doctor experienced in the use of anti-cancer medicines will supervise your Lartruvo therapy.

**Premedication**

You will be given medicines to reduce the risk of an infusion-related reaction before you receive Lartruvo.

### **Dose and administration**

The recommended dose of Lartruvo is 15 mg per kilogram of your body weight on days 1 and 8 of each 3-week cycle. Lartruvo is given in combination with the medicine doxorubicin for up to 8 cycles and then it is given on its own. The number of infusions that you receive will depend on how well and for how long treatment with Lartruvo works and how well you feel. Your doctor will discuss this with you.

This medicine is given as an infusion into a vein via a drip. The drip lasts about 60 minutes.

Detailed instructions for your doctor or your nurse on how to prepare Lartruvo infusion are included at the end of this package leaflet (see 'Handling instructions').

### **Dose adjustments**

During each infusion, your doctor or nurse will check for side effects. Your doctor may also give you a smaller dose or delay your dose of Lartruvo if you get serious side effects including a lowering of your white blood cell counts. If you have an infusion-related reaction during treatment, your doctor or nurse may slow down or stop your Lartruvo infusion.

## **4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them. Your doctor will discuss these with you and will explain the risks and benefits of your treatment.

The following side effects have been reported:

### **Infusion reactions**

Lartruvo has been associated with infusion reactions (see section 2 "Warnings and precautions"). **Tell your doctor or nurse immediately if you feel unwell during infusion.** Below is a list of some typical symptoms associated with infusion reactions:

- Feeling faint
- Fever
- Chills
- Flushing
- Shortness of breath

Other symptoms may occur as well (see section 2 "Warnings and precautions"). Your doctor may consider slowing the Lartruvo infusion or interrupting it to manage these symptoms.

**Very common** (may affect more than 1 in 10 people):

- nausea
- pain in your muscles, joints or bones (musculoskeletal pain)
- low white blood cell counts (including neutrophils and lymphocytes which may increase the risk of infection)
- pain or sores in your mouth or throat (mucositis)
- vomiting
- diarrhoea
- headache
- infusion-related reactions

### **Reporting of side effects**

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

## 5. How to store Lartruvo

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer carton and vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C).

Do not freeze or shake the vial.

Keep the vial in the outer carton to protect from light.

Infusion solution: After dilution and preparation, the medicine must be used immediately. If not used immediately, in-use storage times and conditions before use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C and up to an additional 8 hours at room temperature (below 25 °C). Do not freeze or shake the infusion solution. Do not administer the solution if you notice any particulate matter or discoloration.

This medicine is for single use only.

Do not store any unused portion of the infusion solution for reuse. Any unused medicine or waste material should be disposed of in accordance with local requirements.

## 6. Contents of the pack and other information

### What Lartruvo contains

- The active substance is olaratumab. Each millilitre of the concentrate for solution for infusion contains 10 mg of olaratumab.  
Each 19 mL vial contains 190 mg of olaratumab.  
Each 50 mL vial contains 500 mg of olaratumab.
- The other ingredients are mannitol, glycine, L-histidine monohydrochloride monohydrate, L-histidine, sodium chloride (*see section 2 “Lartruvo contains sodium”*), polysorbate 20 and water for injections.

### What Lartruvo looks like and contents of the pack

Lartruvo concentrate for solution for infusion (sterile concentrate) is a clear to slightly opalescent and colourless to slightly yellow liquid supplied in a glass vial with an elastomeric stopper.

It is available in packs of:

- 1 vial of 19 mL
- 2 vials of 19 mL
- 1 vial of 50 mL

Not all pack sizes may be marketed.

### Marketing Authorisation Holder

Eli Lilly Nederland B.V.  
Papendorpseweg 83  
3528 BJ Utrecht  
The Netherlands.

### Manufacturer

Lilly S.A.  
Avda de la Industria, 30  
28108 Alcobendas  
Madrid  
Spain

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Eli Lilly Benelux S.A./N.V.  
Tél/Tel: + 32-(0)2 548 84 84

**България**

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**Suomi/Finland**

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**United Kingdom**

Eli Lilly and Company Limited  
Tel: + 44-(0) 1256 315000

**This leaflet was last revised in < {month YYYY}>.**

This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine.

The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

### **Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>.

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Handling instructions  
Lartruvo 10 mg/mL  
concentrate for solution for infusion  
olaratumab

The following information is intended for healthcare professionals only

Prepare the infusion solution using aseptic technique to ensure the sterility of the prepared solution.

Each vial is intended for single use only. Inspect the contents of the vials for particulate matter and discolouration. The concentrate for solution for infusion must be clear to slightly opalescent and colourless to slightly yellow prior to dilution. If particulate matter or discolouration is identified, the vial must be discarded.

Vials contain 190 mg or 500 mg as a 10 mg/mL solution of olaratumab; calculate the dose and volume of olaratumab needed to prepare the infusion solution. Only use sodium chloride 9 mg/mL (0.9 %) solution for injection as a diluent.

To administer using pre-filled intravenous infusion containers

Based on the calculated volume of olaratumab, aseptically remove the corresponding volume of sodium chloride 9 mg/mL (0.9 %) solution for injection from the prefilled 250 mL intravenous container and transfer the olaratumab medicine into the container to bring the final volume in the container back to 250 mL. Gently invert the container to mix. **DO NOT FREEZE OR SHAKE** the infusion solution. **DO NOT** dilute with other solutions or co-infuse with other electrolytes or medicines.

To administer using empty intravenous infusion containers

Aseptically transfer the calculated volume of olaratumab into an empty intravenous infusion container. Add a sufficient quantity of sodium chloride 9 mg/mL (0.9 %) solution for injection to the container to make the total volume 250 mL. Gently invert the container to mix. **DO NOT FREEZE OR SHAKE** the infusion solution. **DO NOT** dilute with other solutions or co-infuse with other electrolytes or medicines.

Administer via an infusion pump. A separate infusion line must be used and the line must be flushed with sodium chloride 9 mg/mL (0.9 %) solution for injection at the end of the infusion.

Parenteral medicines should be inspected visually for particulate matter prior to administration. If particulate matter is identified, discard the infusion solution.

Discard any unused portion of olaratumab left in a vial, as the product contains no antimicrobial preservatives.

Any unused medicines or waste material should be disposed of in accordance with local requirements.

**Annex IV**

**Scientific conclusions and grounds for the variation to the terms of the marketing authorisation(s)**

## **Scientific conclusions**

Taking into account the PRAC Assessment Report on the PSUR(s) for olaratumab, the scientific conclusions of CHMP are as follows:

Based on cases of anaphylactic reaction and anaphylactic shock reported in the post-marketing setting, these adverse drug reactions should be specifically be mentioned under the category of infusion-related reactions in section 4.8 of the SmPC. The frequency of anaphylactic reactions/anaphylactic shock is already calculated as part of grade 3-4 infusion-related reactions in the table of Adverse Drug Reactions (ADRs) in the same section of the SmPC. The current wording of the Package leaflet is considered sufficient to communicate this risk.

The CHMP agrees with the scientific conclusions made by the PRAC.

## **Grounds for the variation to the terms of the marketing authorisation(s)**

On the basis of the scientific conclusions for olaratumab the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing olaratumab is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.