เอกสารกำกับยาสำหรับบุคลากรทางการแพทย์

▼ 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 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 50 mL vial contains approximately 146 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 soft tissue sarcoma (STS) with a histologic subtype for which an anthracycline-containing regimen is appropriate and which is not amenable to curative treatment with radiotherapy or surgery.

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[a]	Management recommendations (any occurrence)
Grade 1-2	• Stop the infusion • Paracetamol, H1 antagonist and dexamethasone should be administered as needed (see premedication section) • Once the reaction has resolved, resume infusion at a 50 % decreased infusion rate.[b] • Monitor patient for worsening of condition. • For subsequent infusions, please see premedication section.
Grade 3-4	• Immediately and permanently discontinue treatment with olaratumab (see section 4.4).

[a] Grade per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03
[b] 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 ≥ 3 non-haematologic toxicity deemed related to olaratumab, the dose of olaratumab should be withheld until toxicity is ≤ 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 / µL 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. The risk of anaphylactic reaction is associated with elevated IgE antibody levels against galactose-α-1-3- galactose. 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 146 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 PDGFRα 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 ≥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 (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 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

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

[a] Refer to NCI CTCAE Criteria (Version 4.03) for each Grade of toxicity

[b] 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.

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 ≥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 ≥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.

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-α (PDGFR-α), expressed on tumour and stromal cells. Olaratumab is a targeted, recombinant, fully human immunoglobulin G subclass 1 (IgG1) monoclonal antibody that specifically binds PDGFR-α, blocking PDGF AA, -BB, and -CC binding and receptor activation. As a result, *in vitro* olaratumab inhibits PDGFR-α pathway signalling in tumour and stromal cells. In addition, *in vivo* olaratumab has been shown to disrupt the PDGFR-α 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-α 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^2) on Day 1 of each 21-day cycle for up to 8 cycles or doxorubicin (75 mg/m^2) 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 ≥ 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^2 in the olaratumab plus doxorubicin arm and 299.6 mg/m^2 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.

Lartruvo ENG SmPC_Proposed 23 May 2018 CDS 20160309 v4

Table 3. Summary of survival data – ITT population

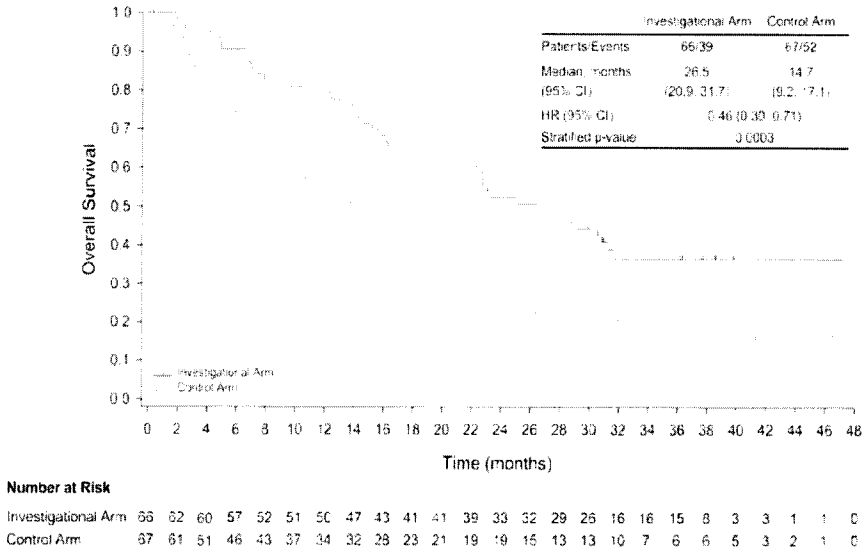
	Lartruvo plus doxorubicin (n = 66)	**Doxorubicin alone (n = 67)**
Progression free survival, months*		
Median (95 % CI)	6.6 (4.1, 8.3)	4.1 (2.8, 5.4)
Hazard ratio (95 % CI)	0.672 (0.442, 1.021)	
p-value	0.0615**	
Overall survival, months		
Median (95 % CI)	26.5 (20.9, 31.7)	14.7 (9.2, 17.1)
Hazard ratio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

Abbreviations: CI = confidence interval

* By investigator assessment

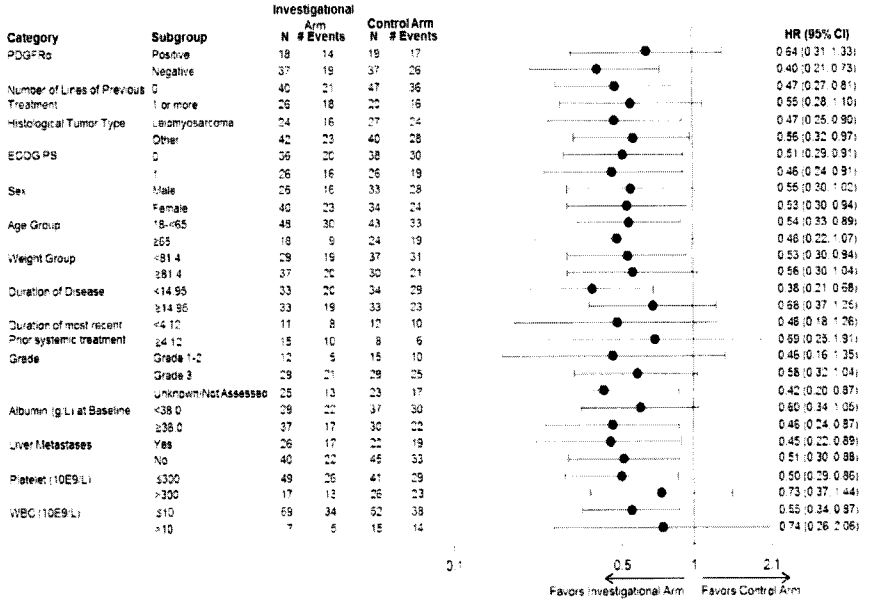
**Met phase 2 protocol defined significance level of 0.19

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



Lartruvo ENG SmPC_Proposed 23 May 2018 CDS 20160309 v4

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 (Vss) 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 ≥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 ≤ 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- α 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 and therefore 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 using acceptable aseptic techniques. 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

19mL 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 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.

Olaratumab infusion solution should be administered via an intravenous line over 60 minutes through a separate infusion line. The line with sodium chloride 9 mg/mL (0.9 %) solution for injection should be flushed 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 Asia, Inc. (Thailand Branch)

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT