CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761038Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type: BLA
Application Number : 761038
PDUFA Goal Date: October 24, 2016
OSE RCM # 2016-500; 2016-502

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Review Completion Date : July 28, 2016
Subject: Review to determine if a REMS is necessary

Established Name: Olaratumab
(Proposed) Trade Name: LARTRUVO
Applicant: Eli Lilly and company

Therapeutic Class: monoclonal antibody
Formulation(s): 500 mg vial
Dosing Regimen: 15 mg/kg IV on day 1 and 8 of each 3-week cycle

Table of Contents

EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) olaratumab (LARTRUVO) is necessary to ensure the benefits of this product outweigh its risks. Eli Lilly and company submitted a Biologic Licensing Application (BLA) 761038 for olaratumab with the proposed indication of in combination with doxorubicin for the treatment of patients with advanced soft tissue sarcoma (STS) not amendable to curative treatment with radiotherapy or surgery. Olaratumab is a platelet-derived growth factor receptor alpha (PDGFR-α) blocking antibody.[1] The risks associated with the use of olaratumab are infusion-related reactions (IRRs), musculoskeletal pain, and neutropenia. The applicant did not submit a proposed REMS or risk management plan with this application.

DRISK and the Division of Oncology Products II (DOPII) agree that a REMS is not needed to ensure the benefits of olaratumab outweigh its risks. Olaratumab is intended to be prescribed by oncologists, and is given via intravenously by nurses who are aware of the risks associated with monoclonal antibodies.

1. Introduction

This review by DRISK evaluates whether a REMS for the NME olaratumab is necessary to ensure the benefits of this product outweigh its risks. Eli Lilly and company submitted a BLA 761038 for olaratumab with the proposed indication in combination with doxorubicin for the treatment of patients with advanced soft tissue sarcoma (STS) not amenable to curative treatment with radiotherapy or surgery. This application is under review in the DOPII. The applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1 PRODUCT INFORMATION

LARTRUVO (olaratumab), a new molecular entity, is a platelet-derived growth factor receptor alpha (PDGFR-α) blocking antibody proposed in combination with doxorubicin for the treatment of advanced soft tissue sarcoma not amenable to curative treatment with radiotherapy or surgery. This application is currently being reviewed under the accelerated approval pathway based on the potential impact on overall survival (OS). Regular approval for this indication will be contingent upon verification and description of clinical benefit in the confirmatory trial. The LARTRUVO (olaratumab) proposed dose is given intravenously 15 mg/kg on days 1 and 8 of each 3-week cycle until disease progression or unacceptable toxicity. For the first 8 cycles, LATRUVO is co-administered with doxorubicin, which is given intravenously on day 1 of each cycle following the LARTRUVO infusion. LARTRUVO is supplied in

[1] Proposed Prescribing Information for Latruvo, dated July 8,2016

500 mg/50 ml vials and is administered by intravenous infusion over 60 minutes. LARTRUVO (olaratumab) is not currently licensed in any jurisdiction.

2.2 Regulatory History

The following is a summary of the regulatory history for LARTRUVO (olaratumab BLA 761038) relevant to this review:

- 02/21/2014: Investigation New Drug (IND) 121500 submission was received.
- 08/21/2014: Fast track designation was granted.
- 10/09/2014: Orphan Drug designation was granted by the Office of Orphan Products Development (OOPD).
- 02/24/2016: BLA 761038 submission, in combination with doxorubicin, for the treatment of patients with advanced soft tissue sarcoma (STS) not amenable to curative treatment with radio therapy or surgery was received. Rolling review and breakthrough designation were granted.
- 06/01/2016: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for LARTRUVO (olaratumab). There is no plan for an Advisory Committee Meeting.

3 Therapeutic Context and Treatment Options

Despite the available chemotherapy options, the prognosis for patients with soft tissue sarcoma remains very poor.

3.1 Description of the Medical Condition[2]

The American Cancer Society estimates that approximately 12,310 new cases of soft tissue sarcoma will be diagnosed in the United States in 2016. Soft tissue sarcoma deaths are expected to be close to 4,990 per year. The current treatment for soft tissue sarcoma is a combination of surgery, radiotherapy, and chemotherapy. The patients with advanced un-resectable or metastatic disease have a particularly poor prognosis, with a median overall survival of 8 to 12 months with treatment. The most frequent histopathologic types of soft tissue sarcoma are leimyosarcoma and liposarcoma which make up 40-50% of all cases of soft tissue sarcoma. The first line treatment is doxorubicin as single agent treatment or combination with ifosfamide. The average response rate is 10-30 %. Refractory treatment includes treatment with dacarbazine, ifosfamide, gemcitabine, taxanes, and pazopanib.

[2] http://www.cancer.org/cancer/sarcoma-adultsofttissuecancer/detailedguide/sarcoma-adult-soft-tissue-cancer-key-statistics (accessed on 7/13/16)

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Summary of Treatment Options Approved by FDA since 2012 Relevant to Proposed Indication as below.

All other available treatments are chemotherapy agents that have adverse effects including bone marrow suppression, nausea, vomiting, hepatic impairment, etc.

Trade Name (Generic)	Approved year	Indication	Dosing/Administration	Safety and Tolerability Issues	REMS
Votrient[3] (pazopanib)	2012	Advanced STS with previous chemotherapy	800 mg oral daily	Hepatotoxicity, QT prolongation, cardiac dysfunction, pneumonitis, arterial & venous thrombo-embolic events.	No REMS, a boxed warning for hepatotoxicity
Yondelis[4] (trabectedin)	2015	Unresectable or metastatic liposarcoma or leio-myosarcoma who received a prior anrthracycline containing regimen	1.5 mg/m2 IV q 3 weeks	Neutropenic sepsis, Rhabdomyolysis, Hepatotoxicity, Cardiomyopathy.	No REMS
Halaven[5] (eribulin)	2016	Unresectable or metastatic liposarcoma with a prior anthracycline containing regimen	1.4 mg/m2 IV day 1 & 8 of a 21-day cycle	Neutropenia, neuropathy, QT prolongation	No REMS

4 Benefit Assessment

The pivotal trial (Trial JGDG) supporting this application consisted of randomized, open-label, multicenter phase 2 trial conducted in the United States. Trial JGDG evaluated the combination of olaratumab with doxorubicin versus doxorubicin alone in 133 patients (control group=67, olaratumab group=66) with advanced soft tissue sarcoma (STS) not amenable to curative treatment with radiotherapy or surgery. The control group was given doxorubicin 75 mg/m2 Intravenously (IV)

[3] Votrient Prescribing Information (last updated 05/2016)

[4] Yondelis Prescribing Information (last updated 10/2015)

[5] Halaven Prescribing Information (last updated 1/2016)

every 21 days for 8 cycles, with option to receive olaratumab monotherapy after progression. The olaratumab group was given olaratumab 15 mg/kg days 1 and 8 plus doxorubicin 75 mg/m2 day 1 every 21 days for 8 cycles, then olaratumab monotherapy until progression. The primary endpoint was progression free survival (PFS) and secondary endpoint is overall survival (OS).

The olaratumab treatment group had median PFS of 6.6 months versus 4.1 months in the control group (HR=0.67; p=0.06). The olaratumab treatment group had overall survival of 26.5 months versus 14.7 months in the control group (HR=0.46, p=0.0003). In the midcycle review meeting, the DOPII clinical reviewers concluded per data available at that time that the applicant provided evidences of effectiveness based on the improvement of PFS and OS in Trial JGDG. However, the magnitude of the clinical benefit is uncertain as assessed by a single trial in a heterogeneous population.[6]

5 Risk Assessment [7]

The most important safety concerns in patients who received olaratumab plus doxorubicin, as compared to doxorubicin alone, were infusion-related reactions (13% vs. 0%), cardiac arrhythmia (16% vs. 15%), cardiac dysfunction (23% vs. 17%), neutropenia (58% vs. 35%), and musculoskeletal pain (64% versus 25%).

Similar to other monoclonal antibodies, olaratumab is associated with the risk of IRRs. The rate of serious (grade 3-4) infusion reactions is about 3 %. Oncologists are familiar with IRRs and manage this risk by giving steroids and antihistamines as necessary. There was one death due to an IRR in a patient who received olaratumab after doxorubicin. That patient did not receive any pre-medication.

Cardiac toxicity is a known adverse event associated with doxorubicin. The rate of cardiac arrhythmias was almost the same in both arms (16% vs. 15%). The incidence of cardiac dysfunction was slightyly higher in the olaratumab arm.

Doxorubicin is a myelosuppressive agent. Although the rate of neutropenia was higher in the olaratumab group, the incidence of febrile neutropenia was similar between the 2 arms (control 12.5% vs. olaratumab 13.3%).

Musculoskeletal pain was higher in the olaratumab arm (64%) compared to the control arm (25%)[8]. The rate of grade 3 and 4 musculoskeletal pain was 8% in the olaratumab arm versus 2% in the control arm. Musculoskeletal pain was managed by providing supportive care and pain medications.

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[6] Drs. Chuk & Doros, DOPII, midcycle clinical review presentation, dated May 20, 2016.

[7] Drs. Chuk & Doros, DOPII, midcycle clinical review presentation, dated May 20, 2016

In Trial JGDG, deaths occurred in 56% of the patients in olaratumab arm and 51% of patients in the control arm. The investigators reported that all deaths in the olaratumab arm were due to disease progression. In the control arm, the investigators reported 5 deaths were due to adverse events (1 patient each with aspirational pneumonia, sepsis, respiratory failure, septic shock, and cardiac arrest). The remainder of the deaths in the control arm were due to disease progression.

Based on animal data and its mechanism of action, olaratumab can cause fetal harm[9]. The Division of Pediatric and Maternal Health (DPMH) recommends that females of reproductive potential should be advised to use effective contraception during treatment with olaratumab and for 3 months following the last dose[10].

There is no data on the presence of olaratumab in human milk. Because of the potential for serious adverse reactions in breastfeeding infants from olaratumab, DPMH recommends that women should be advised not to breastfeed during treatment with olaratumab and for 3 months following the last dose[11].

6 Expected Post-Market Use

It is expected that oncologists will be the primary health care provider to prescribe olaratumab. Olaratumab is expected to be given by infusion nurses at infusion centers or in an oncologist's office. Neutropenia, IRRs, cardiac toxicity, and pain are well-known side effects to oncologists and nurses who are familiar with the management of these events.

There is a very limited patient population expected to receive olaratumab; the proposed indication is STS not amenable to curative treatment with radiotherapy or surgery. Patients receiving olaratumab are expected to be under the care and monitoring of oncologists and nurses for every treatment.

7 Evaluating the Need for a REMS

The most common grade 3 or 4 adverse events of olaratumab were IRRs, neutropenia, and musculoskeletal pain. These events were managed in the clinical trial patient population by giving pre-medications, dose modification, and pain control. Oncologists are familiar with IRRs with this class of product and manage this risk by giving steroids and antihistamines as necessary.

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[9] Proposed Prescribing Information for Lartruvo, 12.1 Clinical Pharmacology, dated July 9, 2016.

[10] Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review from Division of Pediatric and Maternal Health, dated July 21, 2016

[11] Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review from Division of Pediatric and Maternal Health, dated July 21, 2016

Current FDA-approved therapies for the advanced STS are trabectedin and pazopanib. Eribulin is approved to treat patients with unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen. All three of these drugs were approved without a REMS. Their adverse events are communicated in their respective labels under "Warnings and Precautions" and "boxed warning".

- Trabectedin has warnings and precautions of neutropenic sepsis, rhabdomyolysis, hepatotoxicity, cardiomyopathy, and embryofetal toxicity.
- Pazopanib has a boxed warning for severe and fetal hepatotoxicity.
- Eribulin has warnings and precautions of neutropenia, peripheral neuropathy, fetal harm, and QT prolongation.

The sponsor proposes that the adverse events will be communicated in the olaratumab prescribing information under "Warnings and Precautions" and "Adverse Reactions". The sponsor does not propose a boxed warning.

Olaratumab is not currently licensed in any jurisdiction.

At this time we do not believe a REMS is warranted for this product. The safety profile of this product is consistent with the safety profile of other monoclonal antibodies and with other products used to treat STS. Furthermore, it is expected that oncologists will be the primary health care provider to prescribe olaratumab and that olaratumab will be administered at infusion centers or in an oncologist's office by nurses that are familiar with the management of these events.

8 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for olaratumab beyond routine pharmacovigilance and labeling. Lilly states that "Based on current information from the ongoing evaluation of the clinical safety of olaratumab and as summarized in the application, Lilly believes that labeling will adequately communicate safety risks to prescribers." Lilly did not propose a Boxed Warning in the labeling.

9 Conclusion & Recommendations

Based on the available data, DRISK and DOPII agree that risk mitigation measures beyond professional labeling are not warranted for olaratumab and a REMS is not necessary to ensure the benefits outweigh the risks. The risks associated with olaratumab are well known adverse events associated with other oncology treatments and oncologists and nurses are familiar with managing these events.

Should DOPII have any concerns or questions, or feel that a REMS is warranted for this product, or if new safety information becomes available, please send a consult to DRISK.

10 Appendices

10.1 MATERIALS REVIEWED

The following is a list of materials informing this review:

- http://www.cancer.org/cancer/sarcoma-adultsofttissuecancer/detailedguide/sarcoma-adult-soft-tissue-cancer-key-statistics (accessed on 7/13/16)
- Votrient Prescribing Information (last updated 05/2016)
- Yondelis Prescribing Information (last updated 10/2015)
- Halaven Prescribing Information (last updated 1/2016)
- Drs. Chuk & Doros. DOPII, midcycle clinicial review presentation, dated May 20, 2016
- Proposed Prescribing Information for Lartruvo, dated July 8, 2016
- Pregnancy and Lactation Labeling Rule (PLLR) Labeling Review from Division of Pediatric and Maternal Health, dated July 21, 2016

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