[Date]

BY CERTIFIED MAIL AND EMAIL

[Address]

RE: **PRIORITY - Appeal from Coverage Denial [Appeal Number] – Request for Coverage for Mepact® (mifamurtide) for the Treatment of Osteosarcoma for [Patient Name] – [Insurance Coverage Number]**

To Whom it May Concern:

Pursuant to the [Insurer Appeal Program/Policy], this is an appeal from the denial of coverage for Mepact (mifamurtide) for [Patient Name], dated [Date of Coverage Denial]. Mepact (mifamurtide) is medically necessary to treat [Patient Name], who was diagnosed with osteosarcoma on [Date]. [Patient Name] is a covered beneficiary under the [Policy Name], with the identification number [Insurance Coverage Number].

The coverage denial fails to offer substantial evidence that Mepact does not qualify as a medically necessary treatment—and, therefore, a covered treatment—as determined by [Patient Name's] treating oncologist[s]. While Mepact is not approved by the U.S. Food and Drug Administration (FDA) for sale in the United States, absence of FDA approval is not dispositive here. Extensive clinical evidence has shown that Mepact is an effective treatment for osteosarcoma; indeed, it is used as a standard-of-care therapy for non-metastatic osteosarcoma in 40 countries around the world. In addition to being a recognized and accepted treatment for osteosarcoma, the medical necessity for the use of Mepact to treat [Patient Name] is established by Dr. [Name of Oncologist]. *See* Attachment A. [This medical necessity determination is further supported by Dr. [Name of Second Oncologist], another oncologist assisting with the treatment of [Patient Name]. *See* Attachment B.] The expert medical judgment of the treating oncologists, as well as the weight of the peer-reviewed clinical evidence, support coverage for Mepact for the treatment of [Patient Name]'s osteosarcoma.

The Coverage Denial Ignores Extensive Clinical Evidence Establishing That Mepact Is an Effective Treatment for Osteosarcoma

Mepact, which contains the active ingredient mifamurtide, is an immunostimulant that is administered alongside standard adjuvant chemotherapy in patients with high-grade osteosarcoma. The active ingredient mifamurtide is encapsulated in liposomes, which are designed to target delivery and enhances the compound's ability to activate macrophages and monocytes, as well as reduce the compound's toxicity. Mepact received approval in Europe in 2009, the first new osteosarcoma treatment approved in more than 20 years.

As demonstrated by extensive clinical data, the potential benefits from using Mepact to treat the osteosarcoma of [Patient Name] outweigh the risks, particularly given the severity of this often fatal disease and the lack of safety signals seen with Mepact to date. The European approval of Mepact was based on published clinical trial data that showed Mepact treatment

increased lifespan and decreased the risk of death in osteosarcoma patients. The primary trial supporting approval involved 678 patients and evaluated patient outcomes when Mepact was added to three- or four-drug adjuvant chemotherapy (cisplatin, doxorubicin, and methotrexate with or without ifosfamide). The trial showed that Mepact resulted in a 28% decrease in the risk of patient death (p=0.0313). *See* EMA, Mepact (mifamurtide) *Summary of Product Characteristics*. In addition, 78% of patients survived after six years of follow-up, compared to 70% in the control group. Patients with metastatic disease showed an improvement in five-year overall survival from 40% to 53%. Chou, et al, *Addition of muramyl tripeptide to chemotherapy for patients with newly diagnosed metastatic osteosarcoma*, Cancer 2009; 115: 5339–534. As stated by Dr. Ian Lewis, Professor of Cancer Research at Saint James University in Leeds, England, at the time of Mepact's approval, "Mepact is the first therapy in over 20 years to demonstrate any significant long term survival advantage in osteosarcoma."

The results from the trials that supported approval of Mepact have been presented and analyzed in multiple peer-reviewed publications. For example, one article published in the Journal of Clinical Oncology analyzed the clinical trial data that supported Mepact's European approval, noting that the addition of Mepact to adjuvant chemotherapy "resulted in a statistically significant improvement in overall survival and a trend toward better event-free survival." Meyers, et al, *Osteosarcoma: the addition of muramyl tripeptide to chemotherapy improves overall survival--a report from the Children's Oncology Group*, J. Clin. Oncol. 2008 Feb. 1: 26(4):633-8. Similarly, an article from the journal Pediatric Drugs noted a small cohort of patients with metastatic disease saw similar results to those seen in the Phase 3 trial, concluding that "[b]ased on available data, mifamurtide can be considered for inclusion in treatment protocols for localized osteosarcoma." Frampton, *Mifamurtide – A Review of Its Use in the Treatment of Osteosarcoma,* Ped. Drugs 2010 Jun; 12(3):141-53.

The clinical evidence further shows that the benefits of Mepact outweigh its risks, as the safety profile for the drug does not raise any meaningful concerns. As noted in a 2017 survey of sarcoma treatment options, mifamurtide is "generally well-tolerated." Bleloch, et al, *Managing sarcoma: where have we come from and where are we going?* Ther. Adv. Med. Oncol. 2017 Oct: 9(1): 637-59. Another article describing a non-randomized, patient-access study noted that mifamurtide had a "manageable safety profile." Anderson, et al, *Mifamurtide in metastatic and recurrent osteosarcoma: a patient access study with pharmacokinetic, pharmacodynamic, and safety assessments,* Pediatr. Blood Cancer 2014 Feb.: 61(2): 238-44.

Mepact is Medically Necessary for the Osteosarcoma Treatment of [Patient Name]

In addition to the clinical evidence that establishes that Mepact is an effective osteosarcoma treatment, the recommendation of Dr. [Oncologist Name] [and Dr. [Oncologist Name]] for using Mepact, establishes that Mepact is medically necessary for the treatment of [Patient Name].

The treating oncologist[s], Dr. [Oncologist Name] [and Dr. [Oncologist Name]], [has/have] unequivocally recommended that Mepact be made available to treat [Patient Name]. These physicians in their expert medical judgment believe that the potential benefits of using Mepact outweigh any risks. Mepact has been used as a standard-of-care non-metastatic

osteosarcoma therapy in 40 countries, including the member states of the European Union, for almost a decade. The use of Mepact to treat osteosarcoma is well-established worldwide, and this widespread adoption of Mepact therapy bolsters the expert opinion of the treating oncologist[s].

The medical necessity of Mepact to treat [Patient Name]'s osteosarcoma is further supported by the fact that we are running out of options. [Describe course of therapy to date]. There are no alternative treatments available that, when used in conjunction with chemotherapy, have been shown to reduce the risk of osteosarcoma mortality by 28%. And further [surgery and chemotherapy] will be far more costly than the cost of Mepact. The best course of action for all involved, but most importantly for [Patient Name], is to begin treatment with Mepact immediately.

* * *

In light of this evidence, we request that [Insurer Name] overturn the prior coverage denial and provide coverage for Mepact treatments for [Patient Name]. The peer-reviewed clinical evidence clearly establishes that Mepact (mifamurtide) is an effective and accepted treatment for non-metastatic osteosarcoma. Based on this evidence, Dr. [Oncologist Name] [and Dr. [Oncologist Name]] have recommended treatment with Mepact for [Patient Name]. In their expert medical judgment, the evidence shows that the potential benefits of treatment with Mepact outweigh the risks. In contrast, the coverage denial dated [Date of Denial] provides no expert opinion or clinical evidence to the contrary. The weight of the evidence strongly supports that Mepact is medically necessary to treat this life-threatening disease and must be covered by [Insurance Plan].

Thank you in advance for your prompt attention to this appeal. Please feel free to contact us at [Email Address] or [Phone Number] if you require any additional information.

Sincerely,

[Signatory]