Evidence summary on eribulin in the treatment of soft tissue sarcoma patients with previous treatment of two other chemotherapeutic agents for metastatic disease

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Table 1. List of Abbreviations

Abbreviations	Explanation
mSTS	*Metastatic Soft Tissue Sarcoma*
STS	*Soft Tissue Sarcoma*
MBC	*Metastatic Breast Cancer*
ERG	*Evidence Review Group*
ORR	*Overall response rate*
DCR	*Disease control rate*
CBR	*Clinical benefit rate*
CR	*Complete response*
PR	*Partial response*
SD	*Stable disease*
PD	*Progressive disease*
NE	*[Diagnostic imaging data] Not evaluable*
ADRs	*Adverse drug reactions*

Background

What is metastatic soft tissue sarcoma (mSTS)?

Soft tissue sarcomas (STS) are a rare and heterogeneous group of malignant/cancerous tumors of mesenchymal origin with more than 100 histologic subtypes as determined by the type of cell which develops genetic mutation (WHO, 2013). The most common sign of STS is a noticeable lump or swelling which causes pain when the tumor presses on nerves or muscles. A risk of STS can be inherited genetically or can be developed from exposure to chemicals or radiation. (Mayo Clinic, 2018) Biopsy and imaging tests such as x-rays, MRI, and ultrasound may be employed to detect the sarcoma, which comprises less than 1% of all new cancer cases each year (Fletcher, Bridge, Hogendoorn, & Mertens, 2013). In the Philippines, there are a total of 152 reported STS cases in the year 2020. STS patients comprised 2% of all cancers reported (Care PH, 2020). The true frequency of rare diseases such as STS is challenging because they often go misdiagnosed or undiagnosed (National Organization for Rare Diseases, 2018).

What is the standard of care for mSTS?

The standard treatment options for adult STS includes surgery, radiation therapy, and chemotherapy. From the European Society for Medical Oncology [ESMO] 2021 guidelines, the recommended drugs as second-line treatment for mSTS are as follows:

- Eribulin for liposarcomas *(inferred from cited trial)*
- Pazopanib for non-adipogenic STS
- Trabectedin
- [Dacarbazine + Gemcitabine] and [Gemcitabine + Docetaxel] as second line for individuals pre-treated with doxorubicin

According to the National Comprehensive Cancer Network [NCCN] 2022 guidelines, after the failure of first-line chemotherapy regimen (i.e. anthracycline-based, gemcitabine-based), the recommended **second-line drugs for mSTS** are as follows:

- *Preferred regimens:* eribulin, pazopanib, and trabectedin;
- *Other recommended treatments:* dacarbazine, ifosfamide, temozolomide, vinorelbine, regorafenib;
- *Useful in certain circumstances:* Pembrolizumab.

Further, in the initial scoping review of the Evidence Review Group (ERG) which was followed by a consultation with experts from the Philippine Society of Medical Oncology (PSMO), dacarbazine (*in combination with doxorubicin*) was recommended as both first-line treatment or as monotherapy for second-line treatment for advanced soft-tissue sarcoma with non-specific histologies as presented above.

Among the mentioned second-line drugs for mSTS from the NCCN (2022) and ESMO (2021):

- Dacarbazine, gemcitabine, doxorubicin, ifosfamide, and eribulin are registered at the Philippine FDA
- There are still no drugs listed in the Philippine National Formulary (PNF) that are

specific to first-line treatment for metastatic soft-tissue sarcoma, let alone for second-line therapy. We note, however, that ifosfamide, one of the *Other recommended treatments for second-line mSTS,* is currently listed in the PNF under indication sarcoma in general (i.e., *not specifying metastatic soft-tissue sarcoma*). While dacarbazine, another drug under *Other recommended treatments for second-line mSTS,* is also listed in the PNF, it is listed in the PNF for treatment of metastatic melanoma and Hodgkin's lymphoma.

The following are the indications of the said drugs based on US FDA and MIMS PH:

DRUG	US FDA	MIMS PH
DACARBAZINE	*Approved indication inaccessible*	For soft-tissue sarcoma, given in combination with doxorubicin
IFOSFAMIDE	Indicated for use in combination with certain other approved antineoplastic agents for third-line chemotherapy of germ cell testicular cancer. It should be used in combination with mesna for prophylaxis of hemorrhagic cystitis.	For malignant disease and germ cell testicular carcinoma

The World Health Organization (WHO) Essential Medicines List (EML) - Cancer Medicines Working Group (World Health Organization, 2018) advises using an overall survival interval of at least 4 months for first-line cancer treatment included in their EML. They note that likely benefits of cancer medicines tend to be overestimated when used in clinical practice due to methodological biases and they consider an overall survival of less than 3 months as marginal, because it is likely to be clinically and ethically irrelevant. Moreover, evidence on disease-free or progression-free survival may be considered for medicines with limited information on survival. However, the benefits must be large, validated, and consistent with other evidence.

What is the potential of Eribulin as second-line treatment for mSTS?

Among the preferred second-line regimens for mSTS, eribulin mesylate 500 mcg/mL (1mg / 2 mL) per IV was proposed for inclusion in the PNF. It is not currently listed on the 22nd WHO Essential Medicines List (2021).

Eribulin mesylate is a microtubule inhibitor and a synthetic analogue of the natural product, halichondrin B. It inhibits the growth phase of microtubules and sequesters tubulin into non-productive aggregates. This chemotherapeutic agent is indicated for the following conditions: 1) those with metastatic breast cancer who received prior anthracycline and a taxane in either the adjuvant or metastatic setting, and at least 2 prior chemotherapeutic regimens for metastatic disease, and (2) those with unresectable or metastatic liposarcoma who have received prior anthracycline containing regimen (Osgood, et al, 2017). Randomized controlled trials on eribulin showed improvement in overall survival and progression-free survival among those with unresectable liposarcoma (Osgood, et al, 2017; Demetri, et al, 2017).

According to the 2021 evidence review of ESMO using Magnitude of Clinical Benefit Scale (MCBS) v1.1 score system, eribulin and pazopanib had comparable scores of 3, but trabectedin scored lower with 2.

- Eribulin for liposarcomas [II, A; MCBS Score: 3]
- Pazopanib for non-adipogenic STS [II, A; MCBS Score: 3]
- Trabectedin for advanced STS [I, B; MCBS Score: 2]
- [Dacarbazine + Gemcitabine] and [Gemcitabine + Docetaxel] as second line for individuals pre-treated with doxorubicin [II, B; No MCBS Score]

In the guidelines for interpreting the ESMO-MCBS scores,

- *MCBS:* Scores lower than 4 were interpreted as having ***no substantial benefit***, but the guidelines did not specify the differences in the range of scores.
- *Levels of evidence*
    - I - Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
    - II - Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity
- *Grades of recommendation*
    - A - Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
    - B - Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended

Meanwhile from the 2022 review of the NCCN:

- Among ***preferred drugs*** (i.e., ***eribulin****, pazopanib, and trabectedin*):
    - *Efficacy*: All drugs (***eribulin for liposarcoma,*** pazopanib, trabectedin for liposarcoma and leiomyosarcoma) were deemed comparable with a moderate level of efficacy. Eribulin for other subtypes, and trabectedin for other subtypes was deemed minimally effective *(i.e., no / unknown impact on survival, but sometimes provides control of disease*).
    - *Safety*: All three drugs were evaluated as mildly toxic.
    - *Quality of Evidence*: All drugs (***eribulin for liposarcoma,*** pazopanib, and trabectedin for liposarcoma and leiomyosarcoma) were deemed comparable with a good quality of evidence. ***Eribulin for other subtypes***, and trabectedin for other subtypes had average quality of evidence.
    - *Consistency of Evidence*: All drugs (***eribulin for liposarcoma,*** pazopanib, and trabectedin for liposarcoma and leiomyosarcoma) deemed comparable with mainly consistent evidence. ***Eribulin for other subtypes***, and trabectedin for other subtypes may be consistent (*i.e., few trials or only trials with few patients, whether randomized or not, with some variability in outcome*).
    - *Affordability*: All three drugs were evaluated as expensive.
- Among ***other recommended drugs*** (i.e. dacarbazine, ifosfamide, temozolomide, vinorelbine, regorafenib)
    - *Efficacy*: Four drugs (***dacarbazine,*** temozolomide, vinorelbine, regorafenib) were deemed as minimally effective, while ***ifosfamide*** was deemed moderately effective.
    - *Safety*: Four drugs (***dacarbazine,*** temozolomide, vinorelbine, regorafenib) were rated to be mildly toxic, while ***ifosfamide*** was moderately toxic.

- *Quality of Evidence*: Four drugs (***dacarbazine,*** ifosfamide, temozolomide, and regorafenib) were evaluated as having a good quality of evidence, while one drug (vinorelbine) had lower quality of evidence.
- *Consistency of Evidence*: All five drugs were evaluated as having some variability of evidence.
- *Affordability*: Two drugs (***dacarbazine*** and vinorelbine) were generally inexpensive, two drugs (***ifosfamide*** and temozolomide) were moderately expensive, and one drug (regorafenib) was expensive.

See Annex A for the tabulated recommendations for second-line therapy in mSTS.

The usefulness of cancer medicines differ per patient population, healthcare setting, and the capacity of low- to middle-income countries for health services and delivery of medicines. However, in this report, the appraisal of evidence on the efficacy and safety of eribulin and its comparators were based on limited available data from published sources and medical societies.

This review looked at the efficacy and safety of eribulin against dacarbazine among patients with metastatic soft tissue sarcoma who had previous treatment of two other chemotherapeutic agents. The choice of the comparator for this review was based on the Evidence Review Group (ERG) rapid review of studies to identify and refine the research question on eribulin. A consultation to a panel of stakeholders was held to ensure the applicability of the review in clinical practice which included a resolution to set dacarbazine as the appropriate comparator.

Policy Question

Should eribulin be included in the Philippine National Formulary as second-line treatment for metastatic soft tissue sarcoma?

Research Questions

Clinical efficacy, effectiveness and safety

- Among adults with **metastatic soft tissue sarcoma (mSTS),** what is the **efficacy and effectiveness** of **eribulin as second-line treatment** compared to **dacarbazine**, in terms of (a) overall survival, (b) progression-free survival, (c) clinical benefit rate, and (d) improving quality of life?
- Among **patients diagnosed with mSTS,** what is the **safety** of **eribulin as second-line treatment** compared to **dacarbazine**, in terms of (a) all adverse events, (b) neutropenia, (c) peripheral neuropathy, (d) elevation of transaminases, (e) gastrointestinal disorders, (f) alopecia, (g) and electrolyte abnormalities?
- What are the current local and international clinical practice guidelines on the use of eribulin as second-line treatment of mSTS?

Economic impact

- What is the associated medication cost of using eribulin versus dacarbazine as second-line treatment for patients with mSTS?
- What is the total medication cost for the expected number of patients using eribulin versus dacarbazine?

Ethical, Legal, Social, and Health Systems Impact

- What are the **ethical, legal, social, and health system implications** of introducing eribulin as a second-line treatment for mSTS?

Responsiveness to Disease Magnitude, Severity

Current prevalence/ severity of the disease

According to the 2012-2016 data of Surveillance, Epidemiology, and End Results (SEER) Program of the United States (US) National Cancer Institute, the annual incidence of STS worldwide was 3.5 per 100,000. For 2019, American Cancer Society estimates that there have been 12,750 new soft tissue sarcoma cases in the United States.

In the Philippines, according to the CARE PH Hospital-Based Cancer registry system census, there are a total of 152 reported STS cases in the year 2020. STS patients comprised 2% of all cancers reported(Care PH, 2020)

Efficacy, Effectiveness and safety

The following subsections report the evidence on eribulin based on published evidence on efficacy and effectiveness (part 1), safety (part 2), and local and international clinical practice guidelines (part 3) on the use of eribulin.

According to the FDA Philippines, Eribulin intravenous solution has a Monitored-release Certificate of product registration (MR-CPR). An MR-CPR is given to a drug that is newly introduced to the Philippines, regardless if the drug already has established safety data from international studies or not. Nevertheless, the agency attests, through a letter to the HTAC, that regardless of whether the CPR is an MR or a regular one, the CPR issuance is already an assurance that a drug has gone through a thorough evaluation for safety, quality, and efficacy, according to the FDA Philippines. To supplement this, additional review of Phase IV trial data or real world studies from the proponent are covered in this evidence summary.

For this section, we looked at the review of the Evidence Review Group (ERG), specifically for trial data, and the two studies (Kobayashi et al, 2019; Sakata et al, 2019) submitted by the proponent to capture its real world evidence.

- As for the ERG review, the reviewers did not find any systematic reviews comparing eribulin to dacarbazine in terms of clinical effectiveness or clinical safety. Hence, their inclusion criterion was expanded to include non-systematic reviews. Six articles that satisfied the inclusion and exclusion criteria for this review and contained sufficient data for the analysis were retrieved. Upon review of the included studies in the 6 articles, it was noted that all reported the same measures from a single RCT (Schoffski et al, 2016). Hence, the evidence that will be presented in this report is based only on one RCT by Schoffski et al. (2016) which compares eribulin with dacarbazine.
- As for the two studies submitted by the proponent, only one phase IV observational study (Kobayashi et al, 2019) was identified to be relevant to our research question. The other study (Sakata et al, 2019) was excluded because the population does not match that of the research question.

Overall, this section will discuss the clinical evidence results from two studies - Schoffski et al (2016), and Kobayashi et al, (2019).

Part 1. **Review of published evidence on clinical efficacy and effectiveness**

Schoffski et al, 2016 was a randomized control trial (RCT) comparing the efficacy of eribulin versus dacarbazine and will be discussed in the first subsection on efficacy evidence from trial data. Meanwhile, Kobayashi et al, 2019 was a post-marketing surveillance for the clinical effectiveness of eribulin which will be discussed in the next subsection of effectiveness evidence from real world studies.

1.1. Clinical efficacy from clinical trials

The ERG found only one RCT by Schoffski et al, (2016) which was a Phase 3 trial conducted in the United States. It compared eribulin with dacarbazine in terms of progression-free survival and overall survival. The median follow-up period was 31 months (interquartile range, IQR: 25-34 months) for both the eribulin and dacarbazine treatment arms.

While the outcome *median overall survival* [13.5 months vs 11.5 months, HR 0.77 (95% CI 0.62 – 0.96)] favored eribulin over dacarbazine, this was only based on one RCT by Schoffski (2016). Subgroup analyses were performed among patients with liposarcoma and patients with leiomyosarcoma. The study noted, however, that these subgroup analyses were not powered to draw definitive conclusions. Among patients with liposarcoma, the overall survival for those treated with eribulin compared to dacarbazine [15.6 months vs. 8.4 months, HR 0.51 (95% CI 0.35 – 0.75)]. In comparison, the overall survival for patients with leiomyosarcoma was not significantly different between the two treatment groups [12.7 months vs. 13.0 months, HR 0.93 (0.71–1.20)]. In terms of *median progression free survival,* there is no statistically significant difference between eribulin and dacarbazine [2.6 months vs 2.6 months, HR 0.88 95% CI 0.71 - 1.09]. In terms of *quality of life,* the ERG reported that the exact quantitative measures of the effect were not retrievable. Instead, it mentioned that Schoffski et. al (2016) reported that the health-related quality of life using the Global Health Status scores did not greatly differ between the eribulin and dacarbazine groups. Overall, the reported effectiveness outcomes were based on very low quality evidence using GRADE assessment.

Table 1.
Key Findings on the Review of Published Evidence on the Clinical Effectiveness of Eribulin

Outcome	Results
median Overall survival[1] (OS)	Eribulin group = 13.5 months vs. Dacarbazine group = 11.5 months HR 0.77 [0.62, 0.95] • Eribulin arm had longer median OS than dacarbazine, based on one RCT • The quality of evidence is very low Subgroup analysis: *(Note from the study: Subgroup analyses not powered to draw definitive conclusions)* • Liposarcoma: Eribulin group = 15.6 months vs. Dacarbazine group = 8.4 months, HR 0.51 [0.35, 0.75] • Leiomyosarcoma: Eribulin group = 12.7 months vs. Dacarbazine group = 13.0 months, HR 0.93 [0.71, 1.20]

median Progression free survival (PFS)	Eribulin group = 2.6 months vs. Dacarbazine group = 2.6 months HR 0.88 [0.71, 1.09] ● There is no statistically significant improvement in PFS in the eribulin arm as compared to the dacarbazine arm, based on one RCT ● The quality of evidence is very low
Quality of Life[2]	The study investigators (Schoffski et al, 2016) reported that the overall health-related quality of life using the Global Health Status scores did not greatly differ between the eribulin and dacarbazine group.

[1]Median follow-up period: 31 months (interquartile range: 25-34) for eribulin and dacarbazine
[2]The ERG reported that the exact quantitative results for measures of effect were not retrievable from the study of Schoffski et al. 2016.

1.2. Clinical effectiveness based on real world evidence

Kobayashi et al. (2019) was an interim analysis from a Phase IV trial - a nationwide, multicenter, prospective, observational post-marketing surveillance study conducted in 102 institutions throughout Japan. It showed real-world evidence on the effectiveness and safety of eribulin in treating STS, including rare subtypes. The study included 256 Japanese patients with advanced or metastatic STS who received eribulin treatment and were monitored for the following outcomes for effectiveness: overall response rate (ORR), disease control rate (DCR), and clinical benefit rate (CBR). There were no survival outcomes measured. Response type (complete response [CR], partial response [PR], stable disease [SD], progressive disease [PD], not evaluable [NE]) was assessed using the best imaging data obtained during the study and was determined by individual physicians at each institution using the Response Evaluation Criteria in Solid Tumors guideline version 1.1. In this study, ORR was defined as the combination of CR + PR, DCR as CR + PR + SD, and CBR as CR + PR + SD (≥11 weeks). The median duration of treatment for the study was 10.3 weeks (range: 3.0-58.9 weeks). The patients were monitored for a maximum follow-up period of two years.

Note that only 31.8% of the patients in the post-marketing surveillance of Kobayashi et al. (2019) received eribulin as a second-line treatment. No subgroup analysis of these patients by level of treatment (i.e. first-line, second-line) was available. Hence, the results presented here are for the use of eribulin in general (e.g. first-line, second-line, third-line treatment, or later for metastatic STS), and not specific to the use of eribulin as a second-line treatment. Since this is a post-marketing surveillance study with no comparator arm, no conclusion can be drawn on its relative treatment effect.

Based on the results of the study, eribulin demonstrated antitumor activity in patients with advanced or metastatic STS, with an overall response rate of 7.5%, disease control rate of 42.0%, and clinical benefit rate of 17.7% for all patients.

Table 2.
Key Findings per Effectiveness Outcome (N=226) from Kobayashi et al. (2019)

Effectiveness Outcome	Results	Interpretation
Overall response rate = CR + PR	All subgroups: 7.5% (17/226) Leiomyosarcoma: 7.2% (5/69) Liposarcoma: 3.3% (2/60) Other subtypes (non-L-type): 10.3% (10/97)	17 patients (7.5%) out of 226 had a partial response after 12 weeks of eribulin treatment for all subgroups. Only one participant with adipocytic sarcoma had complete response, and none for the other subgroups.
Disease control rate = CR + PR + SD	All subgroups: 42.0% (95/226) Leiomyosarcoma: 49.3% (34/69) Liposarcoma: 50.0% (30/60) Other subtypes (non-L-type): 32.0% (31/97)	17 patients (7.5%) out of 226 had a partial response, while 78 patients (34.5%) out of 226 achieved stable disease after 12 weeks of eribulin treatment for all subgroups.
Clinical benefit rate = CR + PR + SD (≥ 11 weeks)	All subgroups: 17.7% (40/226) Leiomyosarcoma: 18.8% (13/69) Liposarcoma: 18.3% (11/60) Other subtypes (non-L-type): 16.5% (16/97)	17 patients (7.5%) out of 226 had a partial response, while 23 patients (10.2%) out of 226 achieved stable disease after 11 weeks of eribulin treatment for all subgroups.

Note: No patient had a complete response (CR) to eribulin treatment

Part 2. **Review of published evidence on clinical safety**

2.1. Safety from clinical trials

The ERG review cited the same Phase III RCT by Schoffski et al (2016) conducted in the United States which comparing eribulin with dacarbazine in terms of the following safety outcomes: all-grade adverse events, neutropenia: all-grade and high-grade, neuropathy: all-grade and high grade, and compliance (related to discontinuation from adverse events). The ERG report also listed elevation of transaminases, gastrointestinal disorders, alopecia, and electrolyte abnormalities as safety outcomes to be determined in their objectives. However, no results were found for these outcomes since the ERG study team only found one RCT (Schoffski et al, 2016) for Eribulin that is relevant to the research question. Overall, the reported safety outcomes were based on very low quality evidence, as evaluated by the ERG using the GRADE assessment. Table 3 summarizes the results.

Schoffski et al (2016) revealed that the risk of overall adverse events did not differ between eribulin and dacarbazine (RR 0.99; 95% CI: 0.95, 1.03). However, the study noted that for the eribulin arm, there was an increased risk of all-grade neutropenia (RR 1.85, 95% CI: 1.40, 2.44), as well as high-grade neutropenia (RR 2.27, 95% CI: 1.59, 3.22). The risk of all-grade neuropathy was increased with eribulin (RR 5.70, 95% CI: 2.75, 11.80), but analysis for high-grade neuropathy revealed no difference between the 2 chemotherapeutic agents (RR 8.92, 95% CI: 0.48, 164.73). In addition, discontinuation

from adverse events was not found to be different between eribulin and dacarbazine (RR 1.53, 95% CI: 0.73, 3.20).

Table 3.
Key Finding on the Review of Published Evidence on the Clinical Safety of Eribulin (Schoffski et al, 2016)

Safety Outcome	Results
All-grade adverse events *(risk ratio, RR)*	All-Grade Adverse Events: RR: 0.99 [0.95, 1.03] ● There is no statistically significant difference for all-grade adverse events based on 1 RCT. The 95% confidence interval for "All-grade" crossed the line of no effect (i.e., the value of 1). This means that the observed effect is inconclusive as it ranges from favorable to non-favorable outcomes. ● The quality of evidence is very low.
Neutropenia *(risk ratio, RR)*	All-Grade Neutropenia (Grades 1 to 4): RR: 1.85 [1.40, 2.44] ● The result is statistically significant, based on 1 RCT. The risk of having all-grade neutropenia when taking eribulin is 1.85 times higher vs. dacarbazine. ● The quality of evidence is very low. High-Grade Neutropenia (Grade 3 and Grade 4): RR: 2.27 [1.59, 3.22] ● The result is statistically significant, based on 1 RCT. The risk of having high-grade neutropenia when taking eribulin is 2.27 times higher vs. dacarbazine. ● The quality of evidence is very low.
Neuropathy *(risk ratio, RR)*	All-Grade Neuropathy (Grades 1 to 4): RR: 5.70 [2.75, 11.80] ● The result is statistically significant, based on 1 RCT. The risk of having all-grade neuropathy when taking eribulin is 5.70 times higher vs. dacarbazine. ● The quality of evidence is very low. High-Grade Neuropathy (Grade 3 and Grade 4): RR: 8.92 [0.48, 164.73] ● There is no statistically significant difference for high-grade neuropathy based on 1 RCT. The 95% confidence interval crossed the line of no effect (i.e., the value of 1). This means that the observed effect is inconclusive as it ranges from favorable to non-favorable outcomes. ● The quality of evidence is very low.
Compliance *(risk ratio, RR)*	Compliance (Discontinuation): RR 1.53 [0.73, 3.20] ● The outcome on compliance was related to the outcome on discontinuation from adverse events. The result of the RCT reported no difference in compliance between eribulin and dacarbazine. Moreover, the 95% CI line for this outcome crossed the line of no effect (i.e., the value of 1), making the results for this outcome not significant . ● The quality of evidence is very low.

2.2. Safety profile based on real world evidence

Evidence on real world safety data from Kobayashi et al, 2019 presented adverse drug reactions (ADRs) reported among 255 patients in the safety data set analysis. The primary outcome was the frequency and severity of ADRs. Safety was assessed by AEs regardless of the causal relationship with eribulin. Eribulin demonstrated tolerability in patients with a range of advanced or metastatic tumors including STS.

Overall, eribulin demonstrated tolerability in patients with a range of advanced or metastatic tumors including STS. ADRs of at least grade 3 were reported in 174 patients (68.2%) while serious ADRs were reported in 42 patients (16.5%). The most common ADRs were neutropenia and peripheral neuropathy. There were no ADRs leading to death. The most common ADR leading to treatment discontinuation or dose reduction was myelosuppression. The AEs reported in this study were considered manageable and consistent with the known safety profile for eribulin in Japan. The authors also noted that eribulin was tolerable regardless of the clinical setting and number of previous chemotherapies (up to 11 previous cycles in the study). However, Kobayashi et al, 2019 cites that the frequency of reported AEs in post-marketing surveillance studies is "generally lower than clinical studies" due to reliance on reports coming only from treating physicians.

Table 4.
Key Finding on the Real World Safety of Eribulin (N=255) (Kobayashi et al, 2019)

Safety Outcome	Results	Interpretation
Any Adverse Drugs Reactions (ADRs)	All grades: 211/255 (82.7%) At least grade 3: 174/255 (68.2%)	A total of 211 (82.7%) out of 255 patients reported ADRs. The most common ADRs (those occurring in >10% of patients) were neutropenia, 58.4% (150/255); leukopenia, 57.7% (148/255); lymphopenia, 14.9% (28/255); alanine aminotransferase (ALT) increase, 12.6% (32/255); and aspartate aminotransferase increase, 2.2% (6/255). ADRs ≥grade 3 and having an incidence of >5% (13/255) were neutropenia, 52.6% (134/255); leukopenia, 46.3% (118/255); lymphopenia, 14.5% (37/255); and anemia, 6.7% (17/255).
Serious ADRs	Any serious ADRs: 42/255 (16.5%) Neutropenia: 20/255 (7.8%) Leukopenia 19/255 (7.5%)	Serious ADRs were reported in 42 patients (16.5%). There were no ADRs leading to death. Twenty-seven out of 255 patients (10.6%) experienced ADRs that led to the discontinuation of eribulin. Fifty-five patients out of 255 patients (21.6%) had ADRs that required at least one dose reduction of eribulin.

	Febrile neutropenia 5/255 (2.0%) Anemia 3/255 (1.2%)	There were no significant differences in the number of chemotherapy regimens reported at baseline and the incidence of serious ADRs. No treatment-related deaths were observed.

Part 3. **Review of Guidelines**

Recommendations from those scoped by the ERG (EU) were reviewed by the HTA Unit, and these were further supplemented by additional scoping of six countries / organizations (Canada, UK, WHO, USA, Malaysia, and Australia). The guidelines found in the ERG report were based on the 2018 version of the ESMO EURACAN guidelines. However, the HTA Division adapted the 2021 updated guidelines of the same institution. While recommendations from two countries (Canada and UK) were detected, their review research questions do not match our RQ since both guidelines were specific to breast CA only and did not match the comparator of interest. Of the seven countries/organizations reviewed, only three guidelines (US NCCN, Australian Pharmaceutical Benefits Advisory Committee (PBAC) and the EU ESMO-EURACAN) were found relevant to this evidence review. All three guidelines recommended the use of eribulin for mSTS..

Guideline *(Country, Year of publication)*	**Indication and Recommendation**	**Rating**	**Interpretation**
ESMO - EURACAN (*EU, 2021; pp 1356 - 1357*)	Recommended as of 2021 as an option for patients with liposarcomas	Level of Recommendation: **II**	Drug is **associated with antitumor activity**, but the magnitude of benefit is unknown (ESMO, 2022; p. 15)
		Grade of Recommendation: **A**	Having **evidence derived from retrospective studies** which indicate that the drug has clinically - meaningful benefit with matched drug compared with alteration-negative patients (ESMO, 2022; p. 15)
		ESMO-MCBS v1.1 score of **3**	**No substantial benefit** (based on ESMO fact sheet; p. 1)
PBAC (*Australia, 2016; p. 1*)	Recommended as of 2016 for patients with advanced or metastatic liposarcomas who received prior	No rating of evidence indicated	N/A

	chemotherapy including anthracyclines and ifosfamide		
National Comprehensive Cancer Network *(USA, 2022; p. SARC-F EB-1)*	Recommended as of 2022 as one of the preferred regimens under subsequent lines of therapy for advanced/metastatic STS specifically for *L-type sarcoma (i.e., liposarcoma and leiomyosarcoma)*	Category **1**	Based upon **high-level** evidence, there is uniform NCCN consensus that **the intervention is appropriate** (NCCN, 2021; p. EB-1)
		Efficacy: **3/5**	**Moderately effective**: Modest impact on survival, but often provides control of disease (NCCN, 2021; p. EB-1)
		Safety: **3/5**	**Safety: Mildly toxic:** Mild toxicity that interferes with Activities of Daily Living (ADLs) (NCCN, 2021; p. EB-1)
		Quality of Evidence: **4/5**	**Quality of Evidence: Good quality:** One or more well-designed randomized trials (NCCN, 2021; p. EB-1)
		Consistency of Evidence: **4/5**	**Consistency of Evidence: Mainly consistent:** Multiple trials with some variability in outcome (NCCN, 2021; p. EB-1)
		Affordability: **2/5**	**Expensive** (NCCN, 2021; p. EB-1)
National Comprehensive Cancer Network *(USA, 2022; p. SARC-F; EB-1)*	Recommended as of 2022 as one of the preferred regimens under subsequent lines of therapy for advanced and metastatic STS; specifically for non L-type sarcoma	Category **2A**	Based upon **lower-level** evidence, there is uniform NCCN consensus **that the intervention is appropriate** (NCCN, 2021; p. EB-1)
		Efficacy: **2/5**	**Minimally effective:** No or unknown impact on survival, but sometimes provides control of disease (NCCN, 2021; p. EB-1)
		Safety: **3/5**	**Mildly toxic**: Mild toxicity that interferes with Activities of Daily Living (ADLs) (NCCN, 2021; p. EB-1)
		Quality of	**Average quality:** low quality

		Evidence: **3/5**	randomized trial(s) or well-designed non-randomized trial(s) (NCCN, 2021; p. EB-1)
		Consistency of Evidence: **3/5**	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome (NCCN, 2021; p. EB-1)
		Affordability: **2/5**	**Expensive** (NCCN, 2021; p. EB-1)

Recommendation

Among the recommended second-line drugs for mSTS in the guidelines, only dacarbazine and ifosfamide are listed in the PNF. However, dacarbazine is indicated for metastatic melanoma and Hodgkin lymphoma, while ifosfamide is indicated for sarcomas in general. Of these two, dacarbazine was selected as the comparator in this evidence review based on the scoping review of the ERG and consultation with the expert society.

Based on the evidence review and appraisal, the HTAC does not recommend the **inclusion of eribulin [500mcg/mL (1mg/2mL) solution for injection (IV)] as a second-line treatment of metastatic soft tissue sarcoma (mSTS) in the Philippine National Formulary** based on the following reasons:

- There is no significant clinical benefit on using eribulin compared to dacarbazine. Although the median overall survival with an interval of two (2) months [13.5 months for the eribulin group vs 11.5 months for the dacarbazine group, HR 0.77 (95% CI 0.62 – 0.96)] favored eribulin over dacarbazine, this was only based on one RCT by Schoffski (2016) with a very low quality of evidence. In addition, the WHO (2018) advises using an overall survival interval of at least 4 months for first-line cancer treatment as overall survival of less than 3 months is likely to be clinically and ethically irrelevant.

- In terms of safety, there is an increased risk of the following adverse events in the eribulin arm when compared to dacarbazine, based on a very low quality of evidence: neutropenia (All-Grade, High-Grade), and neuropathy (All Grade). The adverse events reported in the trial are consistent with the adverse events reported in the real-world setting by Kobayashi et al, 2019.

- While the NCCN recommended eribulin as one of the preferred regimens under subsequent lines of therapy for advanced/metastatic STS specifically for L-type sarcoma (i.e., liposarcoma and leiomyosarcoma) and non-L-type sarcoma, the cost and evidence presented in the review are not sufficient to support eribulin's claims in terms of efficacy/effectiveness and safety profile, even when compared with dacarbazine.

References

The references cited in this summary document are lifted from the reference report by the Evidence Review Group unless otherwise specified.

Additional references:

- World Health Organization. (2018). *Pricing of cancer medicines and its impacts.* Retrieved from https://apps.who.int/iris/handle/10665/277190

ANNEX A. COMPARISONS WITH SECOND-LINE DRUGS FOR MSTS IN THE PNF AND AMONG CPGS:

<table>
<tr><th rowspan="2">PNF</th><th colspan="4">Clinical Practice Guidelines</th></tr>
<tr><th><u>ESMO</u>
(As second-line)</th><th colspan="3"><u>NCCN</u>
(As second-line)</th></tr>
<tr><td rowspan="10">Carboplatin - indicated for recurrent soft tissue sarcomas for children</td><td rowspan="10">● Eribulin for liposarcomas [II, A; MCBS Score: 3]
● Pazopanib for non-adipogenic STS [II, A; MCBS Score: 3]
● Trabectedin for advanced STS [I, B; MCBS Score: 2]
● For individuals pre-treated with doxorubicin [II, B; No MCBS Score]:
○ Dacarbazine + Gemcitabine
○ Gemcitabine + Docetaxel</td><td colspan="3">PREFERRED</td></tr>
<tr><td rowspan="5">Pazopanib

Trabectedin (liposarcoma and leiomyosarcoma)</td><td>Efficacy: 3/5</td><td>Moderately effective: Modest impact on survival, but often provides control of disease (NCCN, 2021; p. EB-1)</td></tr>
<tr><td>Safety: 3/5</td><td>Mildly toxic: Mild toxicity that interferes with Activities of Daily Living (ADLs) (NCCN, 2021; p. EB-1)</td></tr>
<tr><td>Quality of Evidence: 4/5</td><td>Good quality: One or more well-designed randomized trials (NCCN, 2021; p. EB-1)</td></tr>
<tr><td>Consistency of Evidence: 4/5</td><td>Mainly consistent: Multiple trials with some variability in outcome (NCCN, 2021; p. EB-1)</td></tr>
<tr><td>Affordability: 2/5</td><td>Expensive (NCCN, 2021; p. EB-1)</td></tr>
<tr><td rowspan="3">Trabectedin (other subtypes)</td><td>Efficacy: 2/5</td><td>Minimally effective: No, or unknown impact on survival, but sometimes provides control of disease (NCCN, 2021; p. EB-1)</td></tr>
<tr><td>Safety: 3/5</td><td>Mildly toxic: Mild toxicity that interferes with Activities of Daily Living (ADLs) (NCCN, 2021; p. EB-1)</td></tr>
<tr><td>Quality of</td><td>Average quality: Low quality randomized trial(s)</td></tr>
</table>

			Evidence: **3/5**	or well-designed non-randomized trial(s) (NCCN, 2021; p. EB-1)
			Consistency of Evidence: **3/5**	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome (NCCN, 2021; p. EB-1)
			Affordability: **2/5**	**Expensive** (NCCN, 2021; p. EB-1)
		OTHER RECOMMENDED		
		Dacarbazine	Efficacy: **2/5**	**Minimally effective:** No, or unknown impact on survival, but sometimes provides control of disease (NCCN, 2021; p. EB-1)
			Safety: **3/5**	**Mildly toxic:** Mild toxicity that interferes with Activities of Daily Living (ADLs) (NCCN, 2021; p. EB-1)
			Quality of Evidence: **3/5**	**Average quality:** Low quality randomized trial(s) or well-designed non-randomized trial(s) (NCCN, 2021; p. EB-1)
			Consistency of Evidence: **3/5**	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome (NCCN, 2021; p. EB-1)
			Affordability: **4/5**	**Inexpensive** (NCCN, 2021; p. EB-1)
		Ifosfamide	Efficacy: **3/5**	**Moderately effective**: Modest impact on survival, but often provides control of disease (NCCN, 2021; p. EB-1)

			Safety: **2/5**	**Moderately toxic:** Significant toxicities often occur but life threatening/fatal toxicity is uncommon; interference with ADLs is frequent (NCCN, 2021; p. EB-1)
			Quality of Evidence: **3/5**	**Average quality:** Low quality randomized trial(s) or well-designed non-randomized trial(s) (NCCN, 2021; p. EB-1)
			Consistency of Evidence: **3/5**	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome (NCCN, 2021; p. EB-1)
			Affordability: **3/5**	**Moderately expensive** (NCCN, 2021; p. EB-1)
		Temozolomide	Efficacy: **2/5**	**Minimally effective:** No, or unknown impact on survival, but sometimes provides control of disease (NCCN, 2021; p. EB-1)
			Safety: **3/5**	**Mildly toxic:** Mild toxicity that interferes with Activities of Daily Living (ADLs) (NCCN, 2021; p. EB-1)
			Quality of Evidence: **3/5**	**Average quality:** Low quality randomized trial(s) or well-designed non-randomized trial(s) (NCCN, 2021; p. EB-1)
			Consistency of Evidence: **3/5**	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome (NCCN, 2021; p. EB-1)
			Affordability: **3/5**	**Moderately expensive** (NCCN, 2021; p. EB-1)

		Vinorelbine	Efficacy: **2/5**	**Minimally effective:** No, or unknown impact on survival, but sometimes provides control of disease (NCCN, 2021; p. EB-1)
			Safety: **3/5**	**Mildly toxic:** Mild toxicity that interferes with Activities of Daily Living (ADLs) (NCCN, 2021; p. EB-1)
			Quality of Evidence: **2/5**	**Low quality:** Case reports or extensive clinical experience (NCCN, 2021; p. EB-1)
			Consistency of Evidence: **3/5**	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome (NCCN, 2021; p. EB-1)
			Affordability: **4/5**	**Inexpensive** (NCCN, 2021; p. EB-1)
		Regorafenib	Efficacy: **2/5**	**Minimally effective:** No, or unknown impact on survival, but sometimes provides control of disease (NCCN, 2021; p. EB-1)
			Safety: **3/5**	**Mildly toxic:** Mild toxicity that interferes with Activities of Daily Living (ADLs) (NCCN, 2021; p. EB-1)
			Quality of Evidence: **3/5**	**Average quality:** Low quality randomized trial(s) or well-designed non-randomized trial(s) (NCCN, 2021; p. EB-1)
			Consistency of Evidence: **3/5**	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome (NCCN, 2021; p. EB-1)

			Affordability: **2/5**	**Expensive** (NCCN, 2021; p. EB-1)
		USEFUL IN CERTAIN CIRCUMSTANCES		
		Pembrolizumab (myxofibrosarcoma)	Efficacy: **2/5**	**Minimally effective:** No, or unknown impact on survival, but sometimes provides control of disease (NCCN, 2021; p. EB-1)
			Safety: **4/5**	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only; little interference with ADLs (NCCN, 2021; p. EB-1)
			Quality of Evidence: **3/5**	**Average quality:** Low quality randomized trial(s) or well-designed non-randomized trial(s) (NCCN, 2021; p. EB-1)
			Consistency of Evidence: **3/5**	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome (NCCN, 2021; p. EB-1)
			Affordability: **1/5**	**Very Expensive** (NCCN, 2021; p. EB-1)
		Pembrolizumab (undifferentiated pleomorphic sarcoma / cutaneous angiosarcoma)	Efficacy: **3/5**	**Moderately effective**: Modest impact on survival, but often provides control of disease (NCCN, 2021; p. EB-1)
			Safety: **4/5**	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only; little interference with ADLs (NCCN, 2021; p. EB-1)
			Quality of Evidence: **3/5**	**Average quality:** Low quality randomized trial(s) or well-designed non-randomized trial(s) (NCCN, 2021; p. EB-1)

			Consistency of Evidence: **3/5**	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome (NCCN, 2021; p. EB-1
			Affordability: **1/5**	**Very Expensive** (NCCN, 2021; p. EB-1)
		Pembrolizumab (undifferentiated sarcomas)	Efficacy: **2/5**	**Minimally effective:** No, or unknown impact on survival, but sometimes provides control of disease (NCCN, 2021; p. EB-1)
			Safety: **4/5**	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only; little interference with ADLs (NCCN, 2021; p. EB-1)
			Quality of Evidence: **2/5**	**Low quality:** Case reports or extensive clinical experience (NCCN, 2021; p. EB-1)
			Consistency of Evidence: **3/5**	**May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome (NCCN, 2021; p. EB-1
			Affordability: **1/5**	**Very Expensive** (NCCN, 2021; p. EB-1)