Ifosfamide Shortage Strategies

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Criteria for activation:

- The absence of the product poses a clear threat of adverse outcomes
- No acceptable substitute is readily available in sufficient quantities
- The duration and national significance of the shortage require clinical recommendations for allocation (note: regional coordination is required to ensure consistency of application of strategies)

Please refer to the CRESTS Medical Product Shortage Framework for information on the basic template and tiers and to the CRESTS Resource Page for further information about the process. Information below will be updated until superseded by definitive guidance or termination of the shortage.

Product (generic name): ifosfamide

Product forms affected: *

- IFEX powder for solution for injection, Baxter, 1 gram, vial, 1 count, NDC 00338-3991-01 – production suspended
- IFEX powder for solution for injection, Baxter, 3 gram, vial, 1 count, NDC 00338-3993-01– production suspended
- Ifosfamide powder for solution for injection, Baxter, 1 gram, vial, 1 count, NDC 10019-0925-01 – production suspended
- Ifosfamide powder for solution for injection, Baxter, 3 gram, vial, 1 count, NDC 10019-0926-02 – production suspended
- Ifosfamide lyophilized powder for injection, Fresenius Kabi, 1 gram, vial, 1 count, NDC 63323-0142-10 – allocation due to increased demand
- Ifosfamide injection, Hikma, 50 mg/mL, 20 mL vial, NDC 00143-9531-01- allocation due to increased demand

- Ifosfamide injection, Hikma, 50 mg/mL, 60 mL vial, NDC 00143-9530-01 – allocation due to increased demand

* From the American Society of Health-System Pharmacists (ASHP) Ifosfamide Injection information page.

Brief Situation Overview

Ifosfamide is used in treatment of multiple cancers, particularly pediatric sarcoma, but also testicular and lymphoma. Dosing is weight-based and usual treatment involves multiple cycles.

A Baxter-contracted manufacturer in Germany stopped production due to inspection issues. Fresenius Kabi and Hikma are alternates but cannot meet demand. The duration of the shortage may extend until at least October 2026, though the timeline for resumption of production is unclear. The U.S. Food and Drug Administration (FDA) continues to explore temporary licensing of other internationally manufactured products for domestic use.

Medications are currently on allocation by distributors with multiple hospitals reporting they will not be able to complete critical treatment regimens with current supply. Both Fresenius Kabi and Hikma are expected to release additional product in the coming weeks, but not in adequate quantities to meet usual use.

CRESTS used information from prior shortages as well as expert opinion to summarize current recommended strategies.

Supply Strategies

- Compounding unlikely to be possible
- Significant dose reduction not possible
    - Rounding down doses may be appropriate to avoid opening a new vial for a fractional dose
- Vial-splitting may be possible in large centers by pooling patient administrations/ scheduling to avoid waste or preparing aliquots per USP 797/800 in a pharmacy cleanroom environment (ISO 5)
- Regional coordination to move doses to patients or vice versa
- Regional coordination to ensure that all hospitals are adopting a proportional level of prioritization (refer to the restriction tiers table later in this document)

Substitution Strategies

- Alternate, essentially equivalent regimen for some malignancies
- Alternate regimens with additional side effects or less efficacious/less studied

Conservation Strategies (should only be implemented when regional coordination for standard treatment fails)

- Prioritize potentially curative treatment
- Consider pausing enrollment in research protocols involving ifosfamide
- Restricted use to certain conditions with high curative potential may be required
- Diagnosis-specific considerations (refer to Table 2) - additional restrictions may be determined by treatment team or regional agreement based on patient/local factors
- Unless diagnosis is identified as a high priority in Tier 3, a review team or other institutional or regional review process should ensure that unique factors justify using ifosfamide
- Consideration of amount of dose required by multiple small patients as opposed to few larger patients (as dosing is based on body surface area) may have ethical validity when considered as a secondary factor but should involve multi-disciplinary discussion including ethics consultation should these situations arise. Pre-emptive withholding of treatment of larger patients for theoretical benefit of multiple others is unjustified.

Tiered Restrictions According to Risk

The tiered system helps assign risk posed by the available strategies, helps ensure common terminology during coordination activities, and supports proportional restrictions on the product in shortage. According to the indication for the product, tiers (Table 1) should be sequentially implemented ranging from:

Table 1. Definition of Tiers for Risk-Based Restrictions

Tier 1 – Moderate Shortage	Tier 2 – Severe Shortage	Tier 3 – Critical Shortage
Restrictions should pose low risk for adverse patient outcome	Restrictions pose moderate risk of complications/adverse outcomes for some patient groups, but the overall risk is low	Restrictions pose significant risk of severe complications/ adverse outcomes and must prioritize those patients who can most benefit

All Tier 2 and 3 shortages should involve regional coordination and information sharing to discuss strategies, balance resources, and ensure consistent tiers are being used (i.e., the patient care strategies are as similar as possible within the region – for example, all hospitals are Tier 3B at a given time).

As shortages worsen, restrictions are implemented in proportion to impact at the facility level. When A, B, etc. designations are included, A should precede adoption of B strategies.

Table 2. Common Indications for Ifosfamide and Allocation Considerations[1]

Indication	Tier 1 - Low Risk	Tier 2 – Limited Potential Adverse Outcomes	Tier 3 - Assumed Adverse Outcomes
All Uses	• Vial-splitting /aliquoting may be possible in large centers by pooling patient administrations/scheduling to avoid waste • Rounding doses down to avoid taking small doses from a new vial (up to 10%)[2] • Regional coordination to move doses to patients or vice versa • Alternate, essentially equivalent regimen (e.g., substitution of cyclophosphamide when appropriate) • Consider resequencing treatment to delay ifosfamide-containing cycles • Restrict palliative uses[3]	• Alternate regimen with additional side effects or unclear but expected near-equivalency • Restrict use to curative intent (may include selected salvage treatment)	3A. Alternate regimen with reduced potential for cure 3B. Restrict to primary treatment use
Sarcoma	• Consider non-ifosfamide regimen where appropriate	• Consider single agent treatment of appropriate soft tissue sarcoma (e.g., doxorubicin)	3A. Restrict use to primary treatment regimens 3B. Reserve for Ewing's sarcoma and other highly responsive tumors
Lymphoma	• Consider non-ifosfamide regimen where appropriate	• Alternate regimen with additional side effects • Prioritize completing curative regimens	3A. Restrict use to primary treatment regimens 3B. Consider reserving for Hodgkin Lymphoma/Non-

[1] Less common regimens (e.g., using ifosfamide for Wilm's tumor or neuroblastoma) and less common tumors (e.g., nongerminomatous germ cell tumors) should be considered on a case-by-case basis.
[2] Refer to Hematology/Oncology Pharmacy Association position statement included in the references.
[3] Note that palliative care involves multi-disciplinary interventions which should continue. Ifosfamide is infrequently used in palliative regimens.

Indication	Tier 1 - Low Risk	Tier 2 – Limited Potential Adverse Outcomes	Tier 3 - Assumed Adverse Outcomes
		• Restrict use to curative intent (may include selected salvage treatment)	Hodgkin Lymphoma initial treatment
Neuroblastoma			
Testicular Germ Cell	• Use non-ifosfamide regimen unless inappropriate	• Consider substitution of cyclophosphamide or bleomycin	• No salvage use

Additional Areas of Discussion/Operational Considerations

Because oncological decisions involve multiple variables including tumor type, burden, and genetic factors, individual consideration of patients through a "gate-keeping" process in Tier 3 should be implemented, with prioritization of those patients most likely to benefit from treatment. Ideally, this would be implemented on a regional level. Smaller facilities may need ethics and subject matter expert support with prioritization to avoid a single treating provider making prioritization decisions whenever possible.

In some cases, it may be appropriate to alternate ifosfamide-containing chemotherapy cycles with regimens that do not include it.

If there is adequate supply to initiate chemotherapy that offers a high likelihood of benefit, the treatment should be started (i.e., initiation should not be deferred anticipating further shortage).

Permission to extend use of sterilely aliquoted product may be beneficial for daily-dosed treatment over 3-5 days.

Additional Considerations

CRESTS is aware that some healthcare system guidance for this shortage includes prioritizing children, independent of prognosis. Though ethically consistent with the "fair innings of life" philosophy, the use of duration of benefit outside short-term survival (also, for example, using quality adjusted life years) as a criterion is not a medical prioritization, but a social one. This social prioritization is not shared by all ethnic groups that may, for example, value treatment of elders over children. During the pandemic, the U.S. Department of Health and Human Services Office of Civil Rights asked several states to re-draft triage criteria to avoid using age as an independent variable where no evidence suggested a difference in short-term outcome. CRESTS does not include non-medical prioritization considerations.

This clinical summary does not address the facility and regional ethical and procedural foundation for ensuring that all patients have as fair access as possible to available resources. For additional information, please refer to:

- ASPR TRACIE CRESTS Resources
- ASPR TRACIE Hospital Crisis Standards of Care Resource Allocation Annex Template
- Minnesota Department of Health Recommendations for Ethical Allocation of Carboplatin and Cisplatin (which has foundational ethical frameworks, an operational information sharing plan, and sample resources for clinicians and patients)

References

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