DRUG NAME: Sirolimus, nanoparticle, albumin-bound (nab®)

SYNONYM(S): sirolimus NAB; ABI-009[1]; *nab*-sirolimus[1]; rapamycin protein-bound nanoparticles (albumin-bound)[1]; *nab*-rapamycin[2]

COMMON TRADE NAME(S): FYARRO (USA)

CLASSIFICATION: miscellaneous

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Sirolimus is a macrocyclic lactone produced by *Streptomyces hygroscopicus*. Sirolimus is a potent mTOR (mammalian target of rapamycin) inhibitor. Because mTOR has been identified as a key regulator of cell growth and proliferation, mTOR is a promising therapeutic target for various tumour types. Sirolimus demonstrates antitumour activity *in vitro* and also potentiates the cytotoxicity of selected chemotherapeutic agents. Sirolimus NAB is a human albumin-bound formulation of sirolimus which was created to overcome the low water solubility of the drug in order to enable its intravenous and intravesical administration. As albumin is also a natural transporter of endogenous hydrophobic molecules across the endothelial cell surface, it can enhance the tumour penetration of drugs bound to it. Sirolimus NAB is an immunosuppressive agent.[1,3]

USES:

Primary uses:
Sarcoma[1,4]

Other uses:
Brain cancer[1]
Colorectal cancer[1]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Contraindications:
- history of hypersensitivity reaction to sirolimus,[1] sirolimus NAB,[1] other rapamycin derivatives,[4] albumin,[4] or other drug provided as an albumin bound nanoparticle (nab) formulation

Caution:
- sirolimus NAB is ***NOT interchangeable*** with other sirolimus formulations and should not be substituted
- ***hypersensitivity reactions***, including anaphylaxis, angioedema, exfoliative dermatitis, and vasculitis have been reported with administration of oral sirolimus and human albumin[4]; monitor for at least 2 h after first infusion and as needed for subsequent infusions[4]; premedication with antihistamines is not required[1]
- ***immunization*** during treatment with sirolimus NAB may be less effective or ineffective; update immunizations prior to treatment if possible[4]
- ***immunization with live vaccines*** during treatment with sirolimus NAB is not recommended due to the risk of infection; patients should also avoid close contact with others who have received live vaccines[4]

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SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials. When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	***anemia*** (19-68%, severe 6-15%)
	leukocytosis (18-41%)
	lymphocytosis (12-82%, severe 3-21%)
	neutropenia (12-35%, severe 24%)
	thrombocytopenia (35-58%, severe 3-18%)
cardiac	***palpitations*** (4%)
	sinus tachycardia (4%)
	supraventricular tachycardia (4%)
	tachycardia (12%)
eye	blurred vision (12%)
gastrointestinal	*emetogenic potential:* moderate[5]
	abdominal pain (29%, severe 6%)
	constipation (12-24%, severe 3%)
	diarrhea (23-47%, severe 3%)
	dry mouth (15%)
	hemorrhoids (12%)
	mucosal inflammation (38%)
	mucositis, stomatitis (63-79%, severe 9-18%); reported most often within 8 weeks[4]
	nausea (19-50%)
	vomiting (24-32%, severe 3-4%)
general disorders and administration site conditions	*extravasation hazard:* none[6]; risk of extravasation following IV injection is unknown; local injection site reactions (e.g., inflammation, redness, and ulceration) occurred following SC injection[1]
	edema, peripheral (26-50%, severe 3%))
	fatigue (27-68%, severe 3%)
	pyrexia (12-24%)
infections and infestations	candidiasis (15%)
	infections (59%, severe 3-12%)
investigations	***alkaline phosphatase increase*** (12-29%)
	ALT increase (26-47%, severe 3%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	amylase increase (15%, severe 3%)
	AST increase (12-32%, severe 3%)
	creatinine (blood) increase (12-82%)
	lipase increase (12%, severe 3-6%)
	weight decrease (38-47%)
metabolism and nutrition	appetite decrease (35-44%)
	dehydration (15%, severe 6%)
	failure to thrive (severe 4%)
	hypercholesterolemia (32-48%, severe 3%)
	hyperglycemia (12-38%, severe 9-12%)[1,4]; including in non-diabetic patients[4]
	hypernatremia (12%)
	hypertriglyceridemia (32%, severe 3%)
	hypoalbuminemia (35%, severe 3%)
	hypocalcemia (15%)
	hypoglycemia (15%)
	hypokalemia (21-44%, severe 6-12%)[1,4]; may require supplementation[4]
	hypomagnesemia (15-42%)
	hyponatremia (24%, severe 3%)
	hypophosphatemia (15-19%, severe 9%))
musculoskeletal and connective tissue	pain (47%, severe 3%)
nervous system	dizziness (12%)
	dysgeusia (29-32%)
	headache (29%)
	peripheral neuropathy (15%)
psychiatric	insomnia (12-21%, severe 3%)
	suicidal ideation (severe 4%)
respiratory, thoracic and mediastinal	cough (12-35%)
	dyspnea (12-15%, severe 4%)
	epistaxis (12%)
	pneumonitis (18-21%)
skin and subcutaneous tissue	alopecia (21-24%)
	dermatitis (29%)
	dry skin (12%)
	nail disorder (12%)

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ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	pruritus (18%)
	rash (23-68%)
vascular	***hemorrhage*** (24%, severe 3%)
	hypertension (18-29%, severe 3%)

Adapted from standard reference[1,4] unless specified otherwise.

INTERACTIONS:

Sirolimus is a known substrate for both CYP3A4 and p-glycoprotein. It is expected that inhibitors of these metabolic pathways will increase sirolimus concentrations and inducers of these metabolic pathways will decrease sirolimus concentrations. Moderate or weak inhibitors of CYP 3A4 may be used concomitantly with sirolimus NAB if the sirolimus NAB dose is reduced to 56 mg/m^2. Avoid concomitant use of either strong inhibitors or inducers of CYP3A4 and p-glycoprotein with sirolimus NAB.[1,4]

SUPPLY AND STORAGE:

Injection: Aadi Bioscience Inc. supplies sirolimus NAB as 100 mg single use (preservative free) vials of lyophilized powder. Each vial contains ~800-900 mg of human albumin as a stabilizer. Refrigerate. Protect from light.[7,8]

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on the current brand used at BC Cancer, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information:

- Filter needles are not required for preparation.[7,8]
- Medical devices containing silicone oil as a lubricant may cause the formation of proteinaceous strands in the reconstituted suspension. To avoid administration of these strands, administer sirolimus NAB using an infusion set incorporating a 15 micron (or larger) filter.[7,8]
- In-line filters with a pore size **less** than 15 microns must NOT be used.[7,8]

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

	BC Cancer administration guideline noted in ***bold***, ***italics***
Subcutaneous	no information found
Intramuscular	no information found
Direct intravenous	no information found
Intermittent infusion[7,8]	***over 30 min***; administer with tubing incorporating a 15 micron filter
Continuous infusion	no information found

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BC Cancer administration guideline noted in ***bold***, ***italics***

Intraperitoneal	no information found
Intrapleural	no information found
Intrathecal	no information found
Intra-arterial	no information found
Intravesical	has been used[1]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count (ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BC Cancer usual dose noted in ***bold, italics***

	Cycle Length:	
Intravenous:	3 weeks[1,3,4]:	100 mg/m^2 (range 30-100 mg/m^2) IV for one dose on days 1 and 8. (total dose per cycle 200 mg/m^2 [range 60-200 mg/m^2])

Dosage in renal failure: no adjustment required[1]

Dosage in hepatic failure[1,4]:

Bilirubin		AST	Dose
≤ULN	and	>ULN	75 mg/m^2
>1-1.5xULN	and	any	75 mg/m^2
>1.5-3xULN	and	any	56 mg/m^2

Dosage in dialysis: no information found

REFERENCES:

1. Aadi Bioscience Inc. ABI-009 (*nab*-Sirolimus) Investigator's Brochure - version 8.0. Pacific Palisades, CA, USA; November 13, 2020
2. AADi-LLC. Study Protocol PEC-001: A phase 2 multi-center investigation of efficacy of ABI-009 (*nab*-rapamycin) in patients with advanced malignant perivascular epithelioid cell tumors (PEComa). Pacific Palisades, CA; June 16, 2015
3. Aadi Bioscience Inc. Pharmacy Manual Protocol PEX-002 (version 3.0): Expanded access for an intermediate-size population for ABI-009 (sirolimus albumin-bound nanoparticles for injectable suspension) in patients with perivascular epithelioid cell tumors (PEComa) or patients with relevant genetic mutations for mTOR pathway activation Version 3.0. Pacific Palisades, CA, USA; June 6, 2019
4. Aadi Bioscience Inc. FYARRO® full prescribing information. Pacific Palisades, CA; 11/ 2021
5. BC Cancer. (SCNAUSEA) Guidelines for Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting in Adults. Vancouver, British Columbia: BC Cancer; 1 July 2020
6. BC Cancer Provincial Systemic Therapy Program. Provincial Systemic Therapy Program Policy III-20: Prevention and Management of Extravasation of Chemotherapy. Vancouver, British Columbia: BC Cancer; 1 March 2021
7. Aadi Bioscience Inc. ABI-009 (*nab*-Sirolimus) Investigator's Brochure - version 10.0. Pacific Palisades, CA, USA; July 27, 2021
8. Aadi Bioscience Inc. Pharmacy Manual Protocol PEX-002 (Version 4.0) Expanded Access for an Intermediate-size Population for ABI-009 (Sirolimus Albumin-bound Nanoparticles for Injectable Suspension) in Patients with Perivascular Epithelioid Cell Tumors (PEComa) or Patients with Relevant Genetic Mutations for mTOR Pathway Activation. Pacific Palisades, CA, USA; July 16, 2021

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