DRUG NAME: Idelalisib

SYNONYM(S): GS-1101, CAL-101[1]

COMMON TRADE NAME(S): ZYDELIG®

CLASSIFICATION: miscellaneous

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

MECHANISM OF ACTION:

Idelalisib is a novel, selective inhibitor of phosphoinositide-3-kinase-delta (PI3Kδ kinase), which is active in the signaling pathways of B-cell malignancies. Idelalisib also inhibits cell-signaling receptors (e.g., B-cell receptor, CXCR4/5 chemokine receptors) that are involved in the migration of B-cells to the lymph nodes and bone marrow. Idelalisib inhibits ATP binding, which results in apoptosis and thereby decreases proliferation of malignant B-cells and primary tumour cells.[2-6]

PHARMACOKINETICS:

Oral Absorption	time to peak: 1.5 h[4]	
Distribution	highly protein bound, not concentration dependent[3]	
	cross blood brain barrier?	no information found
	volume of distribution[4]	23 L
	plasma protein binding	93-94%
Metabolism	hepatic, primarily via aldehyde oxidase; lesser extent via CYP3A and UGT1A4	
	active metabolite(s)	no information found
	inactive metabolite(s)	GS-563117
Excretion	mainly by fecal route	
	urine	15%
	feces	78%
	terminal half life	8 h
	clearance[3]	15 L/h

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:

*Leukemia, chronic lymphocytic

*Lymphoma, non-Hodgkin's

*Health Canada approved indication

Other uses:

SPECIAL PRECAUTIONS:

Caution:

- ***ALT/AST* elevations** are reported; treatment in patients with active hepatitis is not recommended[2,3]
- ***severe diarrhea and colitis*** are reported; avoid in patients with inflammatory bowel disease[2]

Developed: 1 August 2017
Revised: 1 November 2020

- serious and fatal ***infections*** are reported; prophylaxis for opportunistic injections such as ***pneumocystis carinii/jirovecii pneumonia*** and ***cytomegalovirus*** is required for all patients; avoid initiating idelalisib in patients with ongoing systemic bacterial, fungal, or viral infections[7]
- idelalisib has ***phototoxic*** potential; patients should avoid sun exposure or wear sufficient sun protection[7]

Special populations: Patients ***older than 65 years*** may experience more grade 3 and higher adverse events.[2]

Carcinogenicity: A small increase in pancreatic islet cell tumours was noted in carcinogenicity studies using male rats.[8]

Mutagenicity: Not mutagenic in Ames test. Idelalisib is not clastogenic in mammalian *in vitro* chromosome tests but is genotoxic in mammalian *in vivo* chromosome tests.[2]

Fertility: Decreased epididymides and testes weight have been reported in study animals; however no degeneration, loss in spermatogenesis, or adverse effects on mating or fertility parameters were reported.[2]

Pregnancy: Post-implantation loss, lower fetal weights, and skeletal malformations were observed in animal studies. Women of child bearing potential should use contraception during treatment and for one month after stopping treatment. Idelalisib may reduce the effectiveness of hormonal contraceptives.[2]

Breastfeeding is not recommended due to the potential secretion into breast milk.

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, and/or determined to be clinically important .[9,10] When placebo-controlled trials are available, adverse events will generally be included if the incidence is ≥5% higher in the treatment group. **Incidence data in the Side Effects table is based on idelalisib monotherapy data where possible; in some cases, incidence data based on combination therapy with rituximab has been included and is indicated with an asterisk (*).**[1,11]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	febrile neutropenia*(5%)
	hemoglobin decrease (28%, severe 2%)
	lymphocyte decrease/increase* (20-25%, severe 9-18%)
	neutropenia (53%, severe 25%)[2]
	thrombocytopenia (26%, severe 6%)
gastrointestinal	*emetogenic potential: low*[12]
	abdominal pain (16-26%, severe 2%)[2,11]
	diarrhea/colitis (47%, severe 14%); see paragraph following **Side Effects** table
	gastroesophageal reflux disease* (6%)
	intestinal perforation; permanently discontinue treatment[3]
	nausea (29%, severe 1%)
	vomiting (15%, severe 1%)
general disorders and	asthenia (12%, severe 2%)

Developed: 1 August 2017
Revised: 1 November 2020

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
administration site conditions	chills* (21%, severe 2%)
	fatigue (30%, severe 1%)
	pain* (7%)
	peripheral edema (10%, severe 2%)
	pyrexia (28%, severe 2%)
hepatobiliary	***hepatotoxicity*** (14%)[4]; see paragraph following **Side Effects** table
immune system	***allergic reactions***, including anaphylaxis; permanently discontinue treatment
infections and infestations (see paragraph following **Side Effects** table)	bronchitis* (6%, severe 1%)
	sepsis* (8%, severe 7%)
	sinusitis* (8%)
	upper respiratory tract infection* (12%)
	urinary tract infection* (5%)
investigations	alkaline phosphatase increase (22%)[11]
	ALT increase (50%, severe 18%); see paragraph following **Side Effects** table
	AST increase (41%, severe 12%); see paragraph following **Side Effects** table
	bilirubin increase (10%)[11]
	gamma-glutamyltransferase increase* (26%, severe 2%)
	hypertriglyceridemia* (56%, severe 3%)
	weight decrease (14%)[11]
metabolism and nutrition	appetite decrease (16%, severe 1%)
	hyperglycemia* (54%, severe 7%)
	hypoglycemia* (11%)
	hyponatremia* (20%, severe 2%)
nervous system	headache (11%, severe 1%)
	progressive multifocal leukoencephalopathy[8,13,14] (<1%); see paragraph following **Side Effects** table
psychiatric	insomnia (12%)
respiratory, thoracic and mediastinal	cough (29%, severe 1%)
	dyspnea (17%, severe 4%)
	pneumonia*, including ***pneumonitis*** (15-25%, severe 16%)[11]; see paragraphs following **Side Effects** table
skin and subcutaneous tissue	drug reaction with eosinophilia and systemic symptoms (DRESS)[15] (<1%); see paragraph following **Side Effects** table
	night sweats (12%)
	rash (13-21%, severe 3%)[2,11]; see paragraph following **Side Effects** table
	Stevens-Johnson syndrome[15] (<1%); see paragraph following **Side Effects** table

Developed: 1 August 2017
Revised: 1 November 2020

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
	toxic epidermal necrolysis[15] (<1%); see paragraph following **Side Effects** table

Adapted from standard reference[2] unless specified otherwise.

Severe ***cutaneous reactions*** have been reported with idelalisib, including exfoliative dermatitis, drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, and various rashes (e.g., erythematous, generalized, pruritic, maculo-papular). Fatal cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have occurred. Treatment interruption and/or dose reduction may be required to manage rash. Permanently discontinue idelalisib for severe reactions and confirmed cases of SJS, TEN, and DRESS. Idelalisib has been shown to have phototoxic potential in *in vitro* studies. Exposure to sunlight should be minimized until the degree of sun sensitivity is determined. Sufficient sun protection should be utilized.[7,15]

Severe ***diarrhea*** and ***colitis***, including fatalities, have been reported. Diarrhea may have sudden or gradual onset, and may occur months after the start of therapy. Diarrhea related to gastrointestinal infection should be ruled out. Mild diarrhea may be treated with antidiarrheal agents (e.g., loperamide) and diet modifications. Severe diarrhea does not respond well to antidiarrheal agents. Recommended treatment options for moderate to severe diarrhea include dose interruption/reduction, symptomatic treatment such as sulfasalazine, or anti-inflammatory corticosteroids (e.g., budesonide or prednisone), and intravenous fluids and electrolyte replacement if the patient is dehydrated. Permanently discontinue idelalisib for life-threatening diarrhea.[2,5,6]

Asymptomatic ***elevations*** in ***ALT*** and ***AST*** may occur, however serious or fatal ***hepatotoxicity*** has been reported in 14% of patients. Elevated ALT/AST reportedly occurs within the first 12 weeks of treatment and is usually reversible with dose interruption. Resume treatment at a reduced dose; discontinue treatment for recurrent hepatoxicity.[2,5]

Idelalisib has been associated with serious and fatal ***infections***. Infections occur most frequently in the respiratory system or are septic events. Both conventional and opportunistic pathogens have been identified. Idelalisib should not be started in patients with any evidence of ongoing systemic bacterial, fungal, or viral infections. Prophylaxis for opportunistic infections such as *Pneumocystis carinii/jirovecii* pneumonia and cytomegalovirus is required for all patients during treatment and for 2 to 6 months following treatment. Consider patient risk factors such as presence of prolonged neutropenia or concurrent corticosteroid treatment when determining the appropriate length of prophylaxis following treatment. Idelalisib should be permanently discontinued if there is evidence of cytomegalovirus infection or viremia.[7]

Pneumonitis with fatal outcomes has been reported. Time to occurrence is highly variable and may occur a few weeks to over one year from start of treatment. New respiratory symptoms should be promptly reported. For serious pulmonary symptoms, interrupt treatment until the etiology has been determined. If pneumonitis is confirmed, discontinue treatment and administer systemic corticosteroid therapy as appropriate.[2,7]

Progressive multifocal leukoencephalopathy (PML) has been associated with the use of idelalisib. Risk factors include prior or concurrent treatment with immunosuppressive therapies associated with PML. PML should be considered in patients with new or worsening neurological, cognitive, or behavioural signs and symptoms. Idelalisib should be held until PML is excluded, and permanently discontinued if PML is confirmed.[8,13,14]

Developed: 1 August 2017
Revised: 1 November 2020

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
ketoconazole[2,5]	idelalisib C_{max} increased by 25%, AUC increased by 79%	strong CYP3A inhibition by ketoconazole	monitor for signs of toxicity of idelalisib; dose interruption and reduction of idelalisib may be necessary
midazolam[2,3]	midazolam C_{max} increased by 140%, AUC increased by 440%	strong CYP3A inhibition by idelalisib	avoid concurrent therapy
rifampin[2,3]	idelalisib C_{max} decreased by 58%, AUC decreased by 75%	strong CYP3A induction by rifampin	avoid concurrent therapy

Idelalisib is a substrate of CYP 3A4. Strong CYP 3A4 **inducers** may reduce idelalisib concentration; avoid concurrent use if possible. Strong CYP3A4 **inhibitors** may increase idelalisib concentration; monitor for signs of toxicity. Dose interruption and reduction of idelalisib may be necessary.[2-5]

Idelalisib is a strong CYP3A inhibitor; concurrent therapy with CYP3A substrates may increase their exposure. Caution is recommended with substrates with narrow therapeutic index.[2]

Concurrent therapy with aldehyde oxidase inhibitors may increase idelalisib concentrations; clinical significance is unknown.[2]

Idelalisib induces CYP3A4, CYP2C9, and UGT1A1 which are all involved in first-pass metabolism of ethinyl estradiol. Idelalisib may decrease bioavailabilty of ethinyl estradiol by these mechanisms and decrease the effectiveness of hormonal contraceptives.[2]

SUPPLY AND STORAGE:

Oral: Gilead Sciences Inc. supplies idelalisib as 100 mg and 150 mg film-coated tablets. Store at room temperature.[2]

Additional information: Dispense only in ***original container***.[15]

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***

Oral[7,16]: ***150 mg*** (range 100-150 mg) ***PO twice daily***

Administer with food or on an empty stomach.

Concurrent radiation: no information found

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix "Dosage Modification for Myelosuppression"

Developed: 1 August 2017
Revised: 1 November 2020

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

Dosage in renal failure[2]*:* no adjustment required for any degree of renal impairment

Dosage in hepatic failure[2]*:* mild or moderate hepatic impairment: no starting dose adjustment required
severe hepatic impairment : no information found (hepatic impairment may result in increased exposure; monitor for adverse effects)

Dosage in dialysis: no information found

Children: no information found

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