Drug Monograph

A - Drug Name

idelalisib

COMMON TRADE NAME(S): Zydelig™

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B - Mechanism of Action and Pharmacokinetics

Idelalisib is a selective inhibitor of adenosine-5'-triphosphate (ATP) binding to PI3Kdelta kinase, resulting in inhibition of the P13K signalling pathway in malignant B cells.

Absorption	Cmax and AUC increases less than proportional at doses over 100 mg.	
	Effects with food	Food delays absorption (not clinically relevant)
	Peak plasma levels	2 to 4 hours when given after food; 0.5 to 1.5 hours if given when fasting.
Distribution	PPB	93 to 94%
	Cross blood brain barrier?	probable
Metabolism	Main enzymes involved	Primarily via aldehyde oxidase, lesser extent via CYP3A and UGT1A4.
	Inactive metabolites	GS-563117 is inactive against P13Kdelta, but is a strong inhibitor of CYP3A
Elimination	Feces	78%

	Urine	15%
	Half-life	8.2 hours

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C - Indications and Status

Health Canada Approvals:

In combination with rituximab for the treatment of patients with relapsed chronic lymphocytic leukemia (CLL).

Notes:

Effectiveness in combination with rituximab was based on a progression-free survival benefit in a study of relapsed patients not fit to receive cytotoxic therapy with limited follow up.

Decreased overall survival and increased severe adverse events were observed in clinical trials for first line treatment of CLL (with standard therapy) and early line treatment of relapsed indolent NHL. Idelalisib should not be used for first line treatment of CLL or early line treatment of indolent NHL.

Health Canada Conditional Approvals
(pending the result of studies to verify the drug's clinical benefit. Patients should be advised of the nature of the marketing authorization granted.)

As monotherapy for the treatment of patients with follicular lymphoma who have received at least two prior systemic therapies and are refractory to both rituximab and an alkylating agent.

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D - Adverse Effects

Emetogenic Potential: Minimal – No routine prophylaxis; PRN recommended

Extravasation Potential: Not applicable

The following adverse effects were reported from the monotherapy trial in patients with indolent non-Hodgkin lymphoma, or where higher than rituximab plus placebo in patients with CLL.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Dermatological	Rash (21%) (3% severe)	E
Gastrointestinal	Abdominal pain (26%)	E
	Anorexia (16%)	E
	Diarrhea (47%) (14% severe)	E
	Gastroesophageal reflux disease (6%)	E
	Mucositis (6%)	E
	Nausea, vomiting (29%)	I E
General	Edema (10%)	E
	Fatigue (30%)	E
	Fever (28%)	E
Hematological	Myelosuppression ± infection, bleeding (25%) (severe; including opportunistic infections, PML)	E
Hepatobiliary	↕ LFTs (50%) (18% severe)	E
Hypersensitivity	Hypersensitivity (rare)	I E
Metabolic / Endocrine	↑ Triglycerides (56%)	E
Musculoskeletal	Musculoskeletal pain (7%)	E
Nervous System	Headache (11%)	E
	Insomnia (12%)	E
Respiratory	Cough, dyspnea (29%)	E
	Pneumonitis (rare)	E D

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for idelalisib include ↑ LFTs, diarrhea, fatigue, cough, dyspnea, nausea, vomiting, abdominal pain, myelosuppression ± infection, bleeding, rash, anorexia and insomnia.

Increased rates of serious adverse events (mainly infections) and deaths were reported in clinical trials of idelalisib with standard therapies in first line treatment of CLL and early line treatment of

relapsed indolent NHL. Infections included sepsis, febrile neutropenia and opportunistic infections, such as pneumocystis carinii / jirovecii pneumonia (PCP/PJP), cytomegalovirus (CMV) and PML (progressive multifocal leukoencephalopathy). PML has been reported with the use of idelalisib and prior or concomitant immunosuppressive therapies.

Severe **diarrhea** may occur months after starting treatment, respond poorly to antimotility agents, and usually resolves within a few weeks after holding idelalisib and treating with anti-inflammatory agents (e.g. budesonide). IV fluids and electrolytes may be required if dehydration develops. Gastrointestinal infection should be ruled out.

Elevated liver enzymes were observed within 12 weeks of starting treatment, were usually asymptomatic and reversible within 3 to 4 weeks of holding the drug. Recurrences were common despite resuming treatment at a lower dose.

Pneumonitis, including fatal cases, have occurred with variable onset from a few weeks to over a year after starting treatment. If pneumonitis is suspected, idelalisib should be held while the cause is investigated. Discontinue if confirmed as drug-induced.

Severe **skin reactions**, including fatal cases of Steven-Johnson syndrome and toxic epidermal necrolysis have been reported.

Anaphylaxis has been reported as well.

A temporary pharmcodynamic effect of lymphocytosis (≥50% from baseline and absolute lymphocyte count > 5000/mcL) had been observed, and occurred typically within the first 2 weeks of starting idelalisib. In absence of other clinical findings, this should not be considered as progressive disease.

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E - Dosing

Refer to protocol by which patient is being treated.

A supply of loperamide should be provided for diarrhea.

Advise patients to avoid sun exposure or use sufficient sun protection.

Prophylaxis for PCP/PJP is required during treatment and for 2 to 6 months after discontinuation of treatment (duration depending on risk factors such as corticosteroid treatment and prolonged neutropenia).

Adults:

Chronic lymphocytic leukemia (CLL):

idelalisib 150 mg po twice daily in combination with

rituximab (cycle 1: 375 mg/m^2, cycles 2 to 8: 500 mg/m^2)

Follicular lymphoma:

idelalisib 150 mg po twice daily

Dosage with Toxicity:

The table below provides suggested dose modifications for idelalisib. For CLL, refer to the IDEL+RITU regimen monograph for dose modifications for combination therapy.

Dose levels: 150 mg bid, 100 mg bid, discontinue if further dose modification required.

(Continued on the next page)

Toxicity	Grade	Action/idelalisib dose
Diarrhea/colitis	1	Provide supportive care (e.g. loperamide) and continue at the same dose.
	2	Provide supportive care, hold and monitor until resolved to ≤ grade 1. Restart at the same dose.
	3 or 4	Provide supportive care, hold. Consider addition of anti-inflammatory agent (e.g. sulfasalazine, budesonide). Monitor until resolved to ≤ grade 1. Restart at ↓ 1 dose level
Neutropenia Or Thrombocytopenia	3	Continue at the same dose and monitor CBC.
	4	Hold until ANC ≥ 0.5 x 10^9/L and ≥ platelets 25 x 10^9/L. Restart at ↓ 1 dose level
ALT/AST elevation	1 or 2	Continue at the same dose and monitor LFTs.
	3 or 4	Hold until ALT/AST ≤ 1 x ULN. Restart at ↓ 1 dose level Discontinue for recurrent hepatotoxicity.
Pneumonitis / organizing pneumonia	Any grade	Hold and evaluate for respiratory symptoms. • If no infectious origin found and pneumonitis is likely drug-related, discontinue idelalisib. Consider steroids especially if severe. • If infectious origin found, monitor/treat until resolved. Restart at ↓ 1 dose level.
CMV infection/viremia		Discontinue if evidence of CMV infection or viremia (positive PCR or antigen test)
Signs and symptoms of PML	Any	Hold and investigate; refer to neurologist. Discontinue if confirmed.
Signs and symptoms of PCP/PJP		Discontinue
Rash	2	Hold until ≤ grade 1. Restart at the same dose.
	3 or 4	Hold until ≤ grade 1. Restart at ↓ 1 dose level. Discontinue if severe cutaneous reactions or SJS/TEN confirmed and treat appropriately.
Hypersensitivity	3 or 4	Discontinue, treat appropriately.

Dosage with Hepatic Impairment:

AUC is increased with hepatic impairment, but no dosage adjustment is required in mild to moderate hepatic impairment (monitor closely). Insufficient data for patients with severe hepatic impairment. Patients with baseline ALT/AST > 2.5 x ULN or bilirubin > 1.5 x ULN were excluded from clinical trials.

Dosage with Renal Impairment:

No dosage adjustment is required for mild, moderate or severe renal impairment.

Dosage in the elderly:

No dosage adjustment is required for elderly patients. The incidence of severe adverse events was higher among patients aged 65 and older compared to younger patients, but age had no clinically relevant effect on drug exposure.

Children:

Idelalisib is not indicated in patients under 18 years of age. Safety and efficacy have not been established.

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F - Administration Guidelines

- May be administered with or without food

- If a dose is missed, it may be taken within 6 hours of the missed dose. If a dose is missed by more than 6 hours, it should not be taken; the next dose should be taken as scheduled.
- Dispense only in original container with intact seal
- Store below 30^{o}C

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G - Special Precautions

Contraindications:

- in first line CLL and early line indolent NHL outside of a clinical trial
- patients who have a hypersensitivity to this drug or any of its components

Other Warnings/Precautions:

- idelalisib should not be started in patients with any evidence of ongoing systemic bacterial, fungal or viral infections.
- not recommended in patients with ongoing inflammatory bowel disease given the risk of severe diarrhea
- not recommended in patients with active hepatitis or liver disease

Other Drug Properties:

- Carcinogenicity:
  A small increase in pancreatic islet cell tumours was observed in animal studies.
- Phototoxicity: Yes

Pregnancy and Lactation:

- Genotoxicity: Yes
- Embryotoxicity: Yes
- Fetotoxicity: Yes
- Teratogenicity: Yes
  Idelalisib is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 1 month after the last dose.
  Idelalisib may reduce the effectiveness of hormonal contraceptives (refer to drug interactions). Consider additional alternative methods of contraception.

- Excretion into breast milk: Unknown
  Breastfeeding is not recommended.
- Fertility effects: Likely

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H - Interactions

Idelalisib is primarily metabolized by aldehyde oxidase and is a substrate for CYP3A. Its major metabolite, GS-563117, is an irreversible inhibitor of CYP3A. Therefore drug interactions are possible with CYP3A inducers, inhibitors and substrates.

AGENT	EFFECT	MECHANISM	MANAGEMENT
CYP3A4 inducers (i.e. phenytoin, rifampin, dexamethasone, carbamazepine, phenobarbital, St. John's Wort, etc)	↓ idelalisib concentration and/or efficacy (co-admin with rifampin ↓ AUC by 75%)	↑ metabolism of idelalisib	Avoid strong CYP3A inducers
CYP3A4 inhibitors (i.e. ketoconazole, clarithromycin, ritonavir, fruit or juice from grapefruit, Seville oranges or starfruit)	↑ idelalisib concentration and/or toxicity (co-admin with ketoconazole ↑ AUC by 79%)	↓ metabolism of idelalisib	Avoid strong CYP3A inhibitors, if possible. It not possible, monitor for toxicity.
CYP3A4 substrates (e.g. cyclosporine, pimozide, tacrolimus, triazolo-benzodiazepines, dihydropyridine calcium-channel blockers, certain HMG-CoA reductase inhibitors)	↑ substrate exposure and toxicity (co-admin with midazolam ↑ AUC by 440%)	idelalisib is a strong CYP3A inhibitor	Caution and monitor with CYP3A substrates with narrow therapeutic indices
Aldehyde oxidase inhibitors (e.g. raloxifene)	↑ idelalisib concentration and/or toxicity	↓ metabolism of idelalisib	Caution and monitor. Clinical relevance unknown.
CYP2C8 substrates (i.e. paclitaxel, sorafenib,	↑ substrate exposure and toxicity	idelalisib inhbits CYP2C8 in vitro	Caution and monitor. Clinical relevance unknown.

amiodarone)			
CYP2B6, CYP2C9 and CYP2C19 substrates (e.g. warfarin, phenytoin)	↓ substrate exposure and effect	idelalisib induces these isoenzymes in vitro	Caution and monitor with substrates with narrow therapeutic indices
Oral contraceptives	↓ effect of oral contraceptives containing ethinyl estradiol (theoretical)	idelalisib induces isoenzymes involved in first pass metabolism of ethinyl estradiol	Caution. Consider alternative method of contraception.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CMV PCR/Antigen	Regular
Liver function tests	Baseline, every 2 weeks for the first 3 months, thereafter every 1 to 3 months, and as clinically indicated. Weekly with hepatotoxicity until within ULN.
CBC	Baseline, every 2 weeks for the first 6 months, and at least weekly with grade 3 or 4 myelosuppression.
Clinical toxicity assessment for GI, skin, respiratory toxicity, hypersensitivity, bleeding and infection (including opportunistic, CMV)	At each visit

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Supplementary Public Funding

Exceptional Access Program (EAP Website)

- idelalisib - For the treatment of relapsed chronic lymphocytic leukemia, in combination with rituximab, according to specific clinical criteria

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K - References

Furman RR, Sharman JP, Coutre SE, et al. Idelalisib and rituximab in relapsed chronic lymphocytic leukemia. N Engl J Med. 2014 Mar 13;370(11):997-1007.

Gopal AK, Kahl BS, de Vos S, et al. PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med. 2014 Mar 13;370(11):1008-18.

Markham A. Idelalisib: first global approval. Drugs. 2014 Sep;74(14):1701-7.

Zydelig (idelalisib) product monograph. Gilead Sciences Canada, Inc. February 21, 2018.

June 2019 Updated emetic risk category.

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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