DRUG NAME: Imiquimod

SYNONYM(S):

COMMON TRADE NAME(S): ALDARA® P

CLASSIFICATION: immune response modifier

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

MECHANISM OF ACTION:

Imiquimod is a synthetic Toll-like receptor 7 (TLR7) agonist which stimulates innate and cell-mediated immunity to induce antitumour effects. Activation of TLR7 on plasmacytoid dendritic cells, Langerhans cells, and macrophages increases production of inflammatory cytokines such as tumour necrosis factor-α, interferon-α, and interleukin-12 and augments antigen processing and presentation.[1-3]

PHARMACOKINETICS:

Absorption	minimal percutaneous absorption through intact skin; systemic absorption through affected skin is dependent on surface area of application	
Distribution	no information found	
	cross blood brain barrier?	no information found
	volume of distribution	no information found
	plasma protein binding	no information found
Metabolism	metabolites are products of ring hydroxylation, alkyl hydroxylation, or both[4]	
	active metabolite(s)	S26704 and S27700[5]
	inactive metabolite(s)	unnamed[4]
Excretion	half-life following topical administration is ~10x greater than that following SC dosing, suggesting prolonged retention in the skin	
	urine	< 0.9% as unchanged drug and metabolites[2,4]
	feces	< 0.9%
	terminal half life	26 h (following topical administration)
	clearance	no information found

Adapted from standard reference[2] unless specified otherwise.

USES:

Primary uses:
*Basal cell carcinoma

Other uses:
Lymphoma, cutaneous[6-8]
Melanoma[9-11]

*Health Canada approved indication

SPECIAL PRECAUTIONS:

Caution:
- pre-existing ***autoimmune conditions*** and ***inflammatory conditions of the skin***, including chronic graft versus host disease, may be exacerbated by imiquimod[2]
- concurrent ***corticosteroid*** use may potentially limit efficacy of imiquimod[2]
- **delay** imiquimod application until treatment area has healed from previous drug or surgical treatment [12]

- imiquimod may weaken ***condoms*** and vaginal ***diaphragms***[12]
- avoid application to adjacent ***mucosal tissue***; may cause intense pain and swelling[12]

Special populations: Safety and efficacy has not been established in immunosuppressed patients.[12]

Carcinogenicity: In animal studies, imiquimod shows no evidence of carcinogenicity and no effect on tumour development. In photocarcinogenicity studies, the vehicle cream alone decreases time to skin tumour development. Addition of imiquimod to the vehicle cream does not increase carcinogenic risk.[2]

Mutagenicity: Not mutagenic in Ames test and mammalian *in vitro* mutation test. Imiquimod is not clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.[2]

Fertility: No reproduction impairment has been reported in animal studies.[2]

Pregnancy: Imiquimod was not teratogenic in animal studies. Reduced pup weights and delayed ossification were observed in rats with maternally toxic doses.[2]

Breastfeeding is not recommended due to the potential secretion into breast milk.[2]

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.[13,14]

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
blood and lymphatic system/ febrile neutropenia	lymphadenopathy (2-3%)
gastrointestinal	*emetogenic potential:* none[15]
	diarrhea (1-3%)
	nausea (1%)
	vomiting (1%)
general disorders and administration site conditions (see paragraph following **Side Effects** table)	***local skin and application site reactions*** (28-87%, severe 2-31%)
	fatigue (1-2%)
	fever (1-2%)
	flu-like symptoms (1-3%)
infections and infestations	treatment site infection (2%)
musculoskeletal and connective tissue	back pain (1-4%)
	myalgia (1%)
nervous system	headache (4-8%)

Adapted from standard reference[2] unless specified otherwise.

Flu-like symptoms including malaise, fever, nausea, myalgia, and rigors may occur. These reactions can accompany or precede local inflammatory reactions. Temporary dose interruption may be required.[2,12]

Mild to moderate ***local skin reactions*** such as erythema, itching, burning, erosion, excoriation/flaking, and edema commonly occur***.*** Frequency and intensity of reactions may increase with increasing number of weekly applications and reactions may extend beyond the application site onto surrounding skin. Treatment interruption may be required for severe reactions (e.g., if symptoms restrict daily activity or continued application of cream causes intense pain). Severe local skin reaction can be managed with removal of the cream by washing the treatment area with mild soap and water. Imiquimod treatment may be resumed after the skin reaction has subsided. Localized hypopigmentation and hyperpigmentation can occur and may be irreversible. Use imiquimod following previous drug or surgical treatment only after the proposed treatment area has healed, as imiquimod can exacerbate inflammatory skin conditions. Discontinue imiquimod if hypersensitivity reactions (urticaria) or erythema multiforme occurs. Exposure to natural or artificial sunlight should be minimized because of heightened susceptibility to sunburn. In the event of sunburn, hold imiquimod until skin has fully recovered. Patients who develop treatment site infections may require antibiotics and a rest period off imiquimod.[2,16]

INTERACTIONS: none known[2]

SUPPLY AND STORAGE:

Topical: Valeant Canada LP supplies imiquimod as a 5% cream in single-use packets containing 250 mg of cream and a 7.5 g pump which delivers 235 mg of cream per actuation. Cream base is an oil-in-water vanishing cream. Store at room temperature.[2]

Apotex Inc. supplies imiquimod as a 5% cream w/w in single-use packets containing 250 mg of cream. Store at room temperature.[17]

TOPICAL ADMINISTRATION:

General Instructions[2]:

- Wash treatment area with mild soap and water and dry completely.
- Wash hands before and after cream application.
- Apply a thin layer of cream and rub into skin until cream is no longer visible. Do not occlude application site.
- Do not bathe or shower within 30 minutes of applying cream to the skin.[14]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response, and concomitant therapy.

***Adults*:**

BCCA usual dose noted in ***bold, italics***

Topical:	Application frequency and duration of treatment differ by indication (other dosing regimens have been used): • Apply to affected area of skin ***up to 7 times per week;*** treatment may continue for 1-3 months or be ongoing if effective[6-11,18] • Apply 5 times per week for 6 weeks[2,17]
Dosage in renal failure:	no information found
Dosage in hepatic failure:	no information found

BCCA usual dose noted in ***bold, italics***

Dosage in dialysis: no information found

Children: Safety in children has not been established.[2]

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