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Alitretinoin Gel Therapeutic Cheat Sheet

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TRADE NAME

- Panretin gel 0.1%

GENERIC DOSAGE FORM

- Alitretinoin gel 0.1%

MECHANISM OF ACTION[1]

- Alitretinoin or 9-cis-retinoic acid is an endogenous first-generation retinoid.
- Binds to all subclasses of retinoic acid receptors (RARs) and retinoid X receptors (RXRs).
- Once activated, these receptors function as transcription factors that regulate expression of genes that control cellular differentiation and proliferation in both normal and neoplastic cells.
- Broadly, the effects can be divided into:
  - Anti-inflammatory and immunomodulatory effects
  - Anti-proliferative and apoptotic effects
- Alitretinoin suppresses both chemokine receptor expression and recruitment of inflammatory cells. Further, it can markedly reduce macrophages and activated dendritic cells, two major sources of TNF-alpha, which considerably reduces inflammation.
- The anti-proliferative effect of alitretinoin is related to RAR binding, whereas RXR binding mediate the apoptotic effects. These properties are of particular use for the management of Kaposi's Sarcoma (KS).
- Alitretinoin downregulates expression of IL-6 receptors and reduces the expression of viral encoded oncogenes which are known to populate lesions of KS.
- Alitretinoin inhibits the growth of KS cells in vitro[2].

FDA-APPROVED USE[2]

- Indicated for the topical treatment of cutaneous lesions in patients with AIDS-related Kaposi's sarcoma.
  - Contraindication: Systemic anti-KS therapy required (more than 10 new KS lesions in the prior month), symptomatic lymphedema, symptomatic pulmonary KS, or symptomatic visceral KS).

OFF-LABEL USES[1]

- In case reports, Alitretinoin gel has been found to be useful in the treatment of pyogenic granuloma and the classic form of Kaposi's sarcoma[3].
- To no surprise, in oral form, alitretinoin has been shown efficacious in numerous dermatologic disorders including:
  - Chronic hand eczema
  - Palmoplantar psoriasis
  - Cutaneous lichen planus as well as nail lichen planus
  - Atopic dermatitis
  - Lichen simplex chronicus
  - Cutaneous T-cell lymphoma
  - Pityriasis rubra pilaris
  - Dariers disease
- Oral alitretinoin has a very similar side effect profile to the more commonly used systemic retinoids such as isotretinoin or acitretin and has the same teratogenic effects.

DOSING[2]

- Should initially be applied two times daily to cutaneous KS lesions.
  - Application can be gradually increased to three or four times daily, but this frequency of topical retinoid may be limited by tolerability.
- In the phase 3 clinical trial, patients received treatment for 12 weeks[4].
  - 37% of patients achieved a response[4].
  - Response remained statistically significant between the treatment and placebo group even when accounting for CD4 count, prior KS treatment and concomitant antiretroviral therapy[4].
- Alitretinoin can be continued long term in patients and is a practical management strategy given its safety and ease of use.
- If severe irritation occurs, application can be temporarily discontinued for a few days until the symptoms subside.
- Since unaffected skin can become irritated, application to normal skin around the active areas should be avoided.
- Patient should not apply to or near mucosal sites.
- While sometimes advised to help with absorption, occlusive dressings should not be used with alitretinoin gel.

SIDE EFFECTS ASSOCIATED[2]

- Adverse events almost exclusively occur at the site of application.
- Most of the side effects are typical for topical retinoids and are well known to dermatologists:
  - Erythema, scaling, irritation
  - Burning, pruritus
  - Flaking and desquamation
  - Edema

WARNINGS[2]

- Pregnancy
  - Like other topical retinoids, alitretinoin gel could cause fetal harm if significant absorption were to occur in a pregnant woman and therefore should be avoided.
- Photosensitivity
  - Retinoids as a class have been associated with photosensitivity. There were no reports of photosensitivity associated with the use of alitretinoin gel in the clinical studies.

CONTRAINDICATIONS[2]

- Pregnancy and lactation.
- Hypersensitivity to retinoids or any of the ingredients of the product.

PREGNANCY[2]

- 9-cis-retinoic acid (alitretinoin) has been shown to be teratogenic in rabbits and mice.
- Limb and craniofacial defects were observed when rabbits were exposed to oral doses of alitretinoin.
- Animal reproductive studies with topical alitretinoin have not been conducted and it is not known whether topical application can produce high enough systemic levels to cause similar harm as oral therapy. It is also unknown if systemic exposure is increased when applied to ulcerated lesions or by the duration of therapy.
- Overall, women of childbearing potential should be advised not to become pregnant while using alitretinoin gel.
- It is not known whether alitretinoin or its metabolite are excreted into human milk.
- Given that many drugs are excreted into human milk and because of the adverse reactions possible in nursing infants, mothers should discontinue nursing prior to using the drug.

MONITORING[2]

- No laboratory monitoring is required for use of alitretinoin gel.

REFERENCES:

1. Bubna AK. Alitretinoin in Dermatology-An Update. Indian J Dermatol. 2015 Sep-Oct;60(5):520. doi: 10.4103/0019-5154.164426. PMID: 26538721; PMCID: PMC4601442.
2. *Panretin (alitretinoin) gel 0.1%.* Panretin Package Insert. (n.d.). https://www.accessdata.fda.gov/drugsatfda_docs/label/1999/20886lbl.pdf
3. Morganroth GS. Topical 0.1% Alitretinoin Gel for Classic Kaposi Sarcoma. Arch Dermatol. 2002;138(4):542–543. doi:10.1001/archderm.138.4.533
4. Bodsworth NJ, Bloch M, Bower M, Donnell D, Yocum R; International Panretin Gel KS Study Group. Phase III vehicle-controlled, multi-centered study of topical alitretinoin gel 0.1% in cutaneous AIDS-related Kaposi's sarcoma. Am J Clin Dermatol. 2001;2(2):77-87. doi: 10.2165/00128071-200102020-00004. PMID: 11705307.
5. Fowler JF, Graff O, Hamedani AG. A phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of alitretinoin (BAL4079) in the treatment of severe chronic hand eczema refractory to potent topical corticosteroid therapy. J Drugs Dermatol. 2014 Oct;13(10):1198-204. PMID: 25607554.