

## **KETOCONAZOLE (HIGH DOSE/HDK) GUIDELINES**

(Compiled by Charles (Chuck) Maack – Prostate Cancer Advocate)

Ketoconazole comes into play when the usual androgen deprivation medications, particularly the antiandrogens, show signs of failure by elevating PSA level. Ketoconazole is prescribed to temporarily (sometimes long term, other times short term) slow down the normal processes by which enzymes known as CYP17 can convert the secondary androgens like androstenedione and dehydroepiandrosterone (DHEA) which are made in the adrenal glands into testosterone and dihydrotestosterone (which are hormones that stimulate the growth and proliferation of prostate cancer cells).

(Side note: In that it has been determined that when ketoconazole binds to molecules of CYP17 it can come unbound again, a more recent medication that remains bound, abiraterone acetate/Zytiga, is being tried both in trials and in use since when it binds to a molecule of CYP17, that particular molecule of CYP17 is permanently disabled. See: <http://tinyurl.com/3mjr598>)

**KETOCONAZOLE (High Dose/HDK) guidelines accompanied by HYDROCORTISONE (HC) (OR, SPECIAL NOTE - Dr. Strum now advocates TRIAMCINOLONE (brand name ARISTOCORT) (HOWEVER, I do not believe Aristocort is available in the U.S.) to replace hydrocortisone as the accompaniment to HDK. Dr. Strum comments: "Now what I do is simply use triamcinolone (My Note: provided by a compounding pharmacy) at a dose of 2mg bid (two times per day). I will decrease the dose if facial redness is severe or ankle edema. I have tried to use the 4mg bid dose but none of my patients has been able to tolerate it so far."**

Importance of hydrocortisone when prescribed high-dose ketoconazole (HDK) or low-dose ketoconazole (LDK).

**HDK + HC or LDK** (high-dose ketoconazole plus hydrocortisone). Ketoconazole is an anti-androgen. It works by blocking the hormone receptors on the cancer cells, thus preventing access by cancer-stimulating testosterone. In the advanced stage, prostate cancer cells often acquire an overabundance of additional hormone receptors, with the result that even a minuscule amount of testosterone is sufficient to stimulate proliferation. *The hydrocortisone is needed to replace the steroid lost when the ketoconazole shuts down that production by the adrenal glands.* Some men have great success with taking HDK, and others have great difficulty with the

side effects. Like most of these treatments, we only know if they are effective for a given individual when that person actually takes the drug

HDK is initially prescribed at a dose of 200 mg three times a day for one week, then the dose is increased to 400 mg (two tablets) three times a day thereafter. HC is normally prescribed at a dose of 20 mg with breakfast and 10 or 20 mg with dinner. **HC should be taken with food.** If symptoms suggest HC excess (ankle swelling or diabetes in poor control), the dose may need to be decreased. **NOTE:** Do not abruptly discontinue HC. Always discontinue HC by tapering the dose with the guidance of your physician. This may take several weeks. **(HOWEVER, PLEASE TAKE NOTE of Dr. Strum's change to triamcinolone at 2mg twice daily to replace hydrocortisone when treating with ketoconazole. You should discuss this with your physician).**

Unlike HC, **HDK should be taken on an empty stomach** (30-60 minutes before or at least two hours after food) because HDK requires acidity for dissolution. Stomach acid is needed to enhance HDK absorption (bioavailability). Patients take HDK on an empty stomach so that food there will not act as a buffer and interfere with the absorption of HDK. Moreover, histamine 2 (H-2) receptor [antagonists](#) (e.g. Zantac, Tagamet, Pepcid, Axid) decrease HDK absorption by 75%. Proton-pump inhibitors (Prilosec, Prevacid, Nexium) reduce acid even more. Antacids and Carafate will also interfere with HDK bioavailability. Many other drugs have the potential to interfere with the absorption of HDK by their [anticholinergic](#) side effects that decrease stomach acid. These include, but are not limited to the following (check with your physician):

Artane (trihexyphenidyl)

Levsin (hyoscyamine)

Atrovent (ipratropium)

Levsinex (has hyoscyamine)

Beelith (has magnesium)

Librax (has clidinium)

Bellergal (has belladonna)

Lomotil (has atropine)

Bentyl (dicyclomine)

Pro-Banthine (propantheline)

Cogentin (benztropine)

Robinul (glycopyrrolate)

Cystospaz (hyoscyamine)

Transderm-V (scopolamine)

Ditropan (oxybutynin)

Urised (has hyoscyamine)

Donnatal (has belladonna)

Urispas (has hyoscyamine)

IMPORTANT: If being treated for Alzheimer's Disease with Aricept (Donepezil Hydrochloride), ketoconazole can have a drastic effect on the patient. Accordingly, if prescribed ketoconazole, advise the physician that he/she had better research to recognize the serious effect the combination of Aricept and ketoconazole can have.

If a patient has a medical condition under a doctor's care to lower his stomach acid, taking HDK with Coca Cola or Pepsi (Diet OK), lemonade, orange juice, or 1000 mg Vitamin C is a reasonable option to increase absorption of HDK. Medical Oncologist and clinical researcher, Dr. Snuffy Myers does not recommend grapefruit juice be used in this setting. Grapefruit juice does not effectively acidify the stomach and its impact on ketoconazole has not been documented and may lead to accumulation of HDK resulting in toxic drug levels. A recent study done in patients who were taking acid-reducing drugs showed a 50% increase in ketoconazole bioavailability when it was taken along with a carbonated beverage. **(SPECIAL NOTE: PER DR. STRUM - "I am not sure that I would be dogmatic about grapefruit juice not being used. It would depend on the Keto (Nizoral blood levels that are obtained). It would make a lot of sense if we could routinely get by with low dose keto as suggested by docs like Small but I do not find low dose keto as effective. The ability to prevent keto catabolism would be helpful if we could show a routine way of increasing keto blood levels, thereby increasing PC cell kill & decreasing the amount of Keto a patient would have to take. This would make the drug less expensive."** It should also be kept in mind that as people age, they may produce less stomach acid. This could have an impact on HDK absorption. Therefore, adding 500-1000 mg of ascorbic acid (Vitamin C) may be wise to avoid this concern.

Of additional note: Stephen Strum, MD> I am not a fan of low dose Ketoconazole despite the publication by Eric Small et al. I believe we need to see levels of keto at least at 3.0 mcg/ml.

A question often asked is how rapid is the effect of ketoconazole in reducing the testosterone level? There is a rapid decline within 30 minutes, and 90% reduction within 48 hours.

**AN IMPORTANT CONSIDERATION IF NOT ALREADY PRESCRIBED  
DUTASTERIDE/AVODART:**

**Phase II trial of ketoconazole, hydrocortisone, and  
dutasteride (KHAD) for castration resistant prostate cancer  
(CRPC).**

<http://tinyurl.com/y2grqgn>

**NOTE THIS CONCLUSION:** The response rate was equivalent or superior to historical controls, and time to progression was prolonged compared to published durations of 3.5-8.6 months for K/H. These data indicate that addition of D to further suppress intratumor androgen synthesis may result in improved responses, and support a randomized trial to compare KHAD with standard K/H. Updated data and correlative androgen levels will be available.

Disclaimer: Please recognize that I am not a Medical Doctor. I have been an avid student researching and studying prostate cancer as a survivor and continuing patient since 1992. **The comments or recommendations I make are not intended to be the procedure for you to now follow; rather, they are to be reviewed along with the comments or recommendations of others for your own further research, study, and discussion with the physician providing your prostate cancer care to come to your own, personal conclusion.**