USE OF AVODART IN ANDROGENETIC ALOPECIA OR MALE PATTERN BALDNESS (HAIRLOSS)

SUMMARY

1. The treatment of androgenetic alopecia is not an FDA-approved indication for Avodart (dutasteride). LTherefore, GlaxoSmithKline may not make recommendations on the use of Avodart for the purpose.
2. Avodart inhibits the conversion of testosterone to dihydrotestosterone (DHT) resulting in decreased serum DHT concentrations. By this mechanism, Avodart appears to interrupt a key process in the development of androgenetic alopecia (AGA), also known as male pattern hari loss (MPHL).
3. A phase II, multi-center double blind, placebo controlled study was conducted in 416 males with AGA, ages 21-45 years, to evaluate the dose response relationship of Avodart on hair growth. Repeated doses of Avodart (0.05mg), 0.5mg, and 2.5mg daily) were compated to placebo for 6 months. Safety and tolerability of the varying doses of Avodart and finasteride 5mg daily compared with placebo were also investigated.
4. A dose related increase in hair count was seen at week 12 and 24 in patients receiving Avodart, significant increases were also observed in the finasteride treatment group. The increase in hari count was maintained after the cessation of treatment aw=t week 36 (12 weeks after medication discontinuation) in the Avodart 0.5mg and 2.5mg treatment groups, but not in the finasteride or Avodart 0.05mg and 0.1mg treatment groups.
5. The most common drug-related adverse events were decreased libido experienced by 13% of subjects receiving Avodart 2.5mg/day, followed by headaches experienced by 8% of the Avodart 0.1mg/day group and 6% of the Avodart 0.5mg/day and 2.5mg/day group.
6. No large, prospective clinical trials have evaluated the use of avodart for AGA.
7. Avodart is indicated for the treatment of sympotoatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate to improve symptoms, reduce the risk of acute urinary tetention, and reduce the risk of the neeed for BPH-related surgery. Avodart is contraindicated for use in women and children and for patients with knowhn hypersensitivity to dutasteide, other 5?-reductase inhibitors, or any component of the preparation.

Some information contained in this response may be outside the approved prescribing information for *Avodart* . This response is not intended to offer recommendations for administerin *Avodart* in a manner inconsistent with its approved labeling. In order for GlaxoSmithKline to monitor the safety of avodart, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 888-825-5249. Please consult the Prescribing Information for Avodart.

Background

Androgenetic alopecia (AGA), also known as male pattern hair loss (MPHL), is the most common form of hair loss, affecting approximately 50% of Caucasians over the age of 40 years (1). In males, AGA can begin as early as late adosescence; however, the usual onset is at around the age of 30 years (1). AGA results from naturally circulating androgens which progressively transform large terminal scalp follicles to smaller vellus ones, thus resulting in a visibly less dense scalp (2).
Testosterone is the major circulating androgen in the body, but must be converted to dihydrotestosterone (DHT) via the enzyme 5 a -reductase in order to be active in the skin (3). Studies have shown that men with 5 a -reductase deficiency do not develop AGA (*3,4). Therefore, 5 a -reductase inhibitors have been evaluated for the treatment of AGA due to their ability to inhibit the conversion of testosterone to dihydrotestosterone (3,5). Two isoforms of 5 a -reductase are known, type 1 and type 2. Type 2 is predominately located in human genital tissue. Type 1 is distributed throughout the body, and predominates in the skin and scalp (3).
Avodart is a competitive inhibitor of 5 a -reductase, the enzyme responsible for the conversion of testosterone eo dihydrotestosterone (DHT) in the prostate. It inhibits both enzyme types 1 and 2 and is incdicated for the treatment of symptomatic BPH in men with an enlarged prostate to improve symptoms, reduce the risk of acute urinary retention, and reduce the risk of the need for BPH-related sur4gery. Avodart is contraindicated for use in women and children and for patients with known hypersensitivity to dutatsteride, other 5 a -reductase inhibitors, or any component of the preparation (6).
One clinical trial evaluating the use of *Avodart* in AGA has been conducted and is discussed below. No large, prospective clinical trials have evaluated the use of *Avodart* for this use.

Clinical information

A phase 2, multi-center, double blind, placebo-controlled study was conducted in 416 males with AGA, ages 21 to 45 year, to evaluate the dose response relationship of repeated doses of *Avodart* (0.05mg, 0.1mg,0.5mg, and 2.5mg daily) on hair count compared to placebo for 6 months. Safety and tolerability of the varying doses of Avodart and fiasteridde 5mg daily compared with placebo were also investigated. At the time this study was cnducted, the 1-mg dosage strength of finasteride that is currently approved for the treatment of AGA was not available (7).
Patients were included in this study If they had MPHL defined as type IIIv, IV, or V by the modified Norwood-Hamilton classification and had active hair loss or progression in the size of the balding area withig the past 2 years. Patients were randomized into one of the following xix treatment groups: *Avodart* 0.05mg (n=71), Avodart 0.1mg (n=72), Avodart 0.5mg (n=71), finasteride 5mg (n=70), or placebo (n=64) (7). Patients received oral doses once daily for 24 weeks. The study also included and additional follow-up visit and evaluation of hair count at 36 weeks (12 weeks after double-blind study medication had been stopped) (7).
Efficacy was assessed by measuring hair counts of the vertex region of the scalp susing macrophotographic techniques at baseline, 12 weeks, 24 weeks, and at the follow-up visit at 36 weeks (12 weeks after study medication discontinuation). Ther primary efficacy parameter was the hair count ina 1-inch diameter circle, with a target area of 0.79 square inches, surrounding a tattoo. Results are presented in Table 1 and reflect last observation carried forward (LOCF) (weeks 12 and 24) or at the last visit (ALV) (week 36) analyses of the intent-to-treat population (7).

Table 1: Hair count: change from baseline using 0.79 square inch target area (Intent to Treat Population)*(7)

	Avodart					
Time/Parameter	0.05mg/day	0.1mg/day	0.5mg/day	2.5mg/day	Finasteride 5mg/day	Placebo
Week 12						
N	61	65	59	63	68	57
Mean *	5.0	54.3	71.9	100.4	52.1	-22.9
Mean Difference **	27.9	77.2	94.8	123.3	75.0	-
p-value	0.065	<0.0001	<0.001	<0.001	<0.001	-
Week 24						
n	62	66	63	67	69	58
Mean*	24.8	72.3	95.5	109.8	73.2	-29.6
Mean Difference**	54.4	101.9	125.1	139.5	102.8	-
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	-
Week 36						
N	47	52	51	54	61	46
Mean*	-17.1	16.8	84.3	119.8	13.2	-37.3
	20.2	54.1	121.6	157.1	50.5	-
	0.29	0.004	<0.001	<0.001	0.005	

Mean Difference** p-value						

which are reported as at last visit (ALV) values; * Adjusted for baseline values; ** difference between active treatment and placebo.]

As noted in Table 1, dose-related increases in hair count were seen at 12 and 24 weeks across the Avodart treatment groups. Compared to placebo, these changes were significantly different in all Avodart treatment groups (*P* <0.001) except for in the 0.05 group at week 12 (*P<0.* 065). Hair count change from baselilne in the finasteride group was also significantly greater than the placebo group at both 12 and 24 weeks (*P*< 0.001)(7).

At week 36 (12 weeks after cessation of daily medication), improvement in hair count was maintined at asimilar level to that observed at week 24 in those patients receiving Avodart 0.5mg (35.5 at week 24 and 84.3 at week 36) and 2.5mg (109.9-8 at week 24 and 119.8 at week 36) daily. In contrast, improvement in hair count was not mainteained in those patients receiving finasteride 5mg at week 36 compared to week 24 (73.2 at week 24 and 13.2 at week 36), Advodart 0.05mg (24.8 at week 24 and -17.1 at week 36), or Avodart 0.1mg (72.3 at week 24 and 16.8 at week 36)(7).

Adverse Events

Twenty-five percent (102/416) of subjects experienced a total of 169 adverse events that were classified by the investigator as having a reasonable possibility of being drug-related (7). Those drug-related adverse events having and inceidence > 5% within any treatment group are presented in Tale 2.

Table 2: Percent (%) of Subjects with Drug-Related Adverse Events (> 5% of Subjects Within Any Treatment Group)

			Avodart			
Adverse Event	0.05mg/day N=71	0.1mg/day N=72	**0.5mg/day** N=68	2.5mg/day **N=71**	Finasteride 5mg/day N=70	**Placebo** N=64
Any Adverse Event	18	29	16	32	24	27
Altered (Decreased) Libido	3	3	0	13	4	3
Impotence	1	0	0	0	1	5
Headaches	1	8	6	6	3	3
Nausea and Vomiting	0	0	1	1	0	5
Malaise and Fatigue	1	1	1	7	3	3
Abnormal Liver Function Tests	3	1	0	0	0	5

The most common drug-related adverse event were decreased lilbido experienced by 13% of subjects receiving Avodart 2.5 mg/day followed by headaches, experienced by 8% of the Avodart 0.1mg/day group and 6% by both the Avodart 0.5mg/day and 2.5 mg/day group. There were no serious adverse events that were considered drug-related.

Partner Pregnancies

Five partner pregnancies were reported during the study. One female partner spontaneously aborted (study subject was on placebo) and one had a partial placenta previa with subsequent delivery of a normal male infant (study subject was on Avodart 0.5 mg). The other three pregnancies wee normal and resulted in the births of two males (two subjects on "Avodart 0.5mg and one on Avodart 2.5mg)

and one female (subject on Avodart 2.5mg). None of the infants had genital or other abnormalities at birth (7).

Precaution

Avodart Soft Gelatin Capsules should not be handled by a woman who is pregnant or who may become pregnant because of the potential for absorption of dutasteride and the subsequent potential risk to a developing male fetus. Avodart is contraindicated for use in women. Avodart has not been studied in women because preclinical data suggest that the suppression of circulation levles of dihydrotestosterone may inhibit the development of the external genital organs in a male fetus carried by a woman exposed to dutasteride (6) REV 0704

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