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Date: 8/29/94

TO: DR. M. F. MALKIN

FROM: WORLDWIDE HUMAN HEALTH MARKETING

SUBJECT: **WORLDWIDE MARKETING NEEDS REPORT - FINASTERIDE FOR ANDROGENETIC ALOPECIA IN MEN**

I. PURPOSE

The purpose of this document is to express WHHM's Needs with regard to the development of finasteride for the treatment and prevention of androgenetic alopecia in men.

Specific marketing needs for Japan are not discussed, as the clinical program for Japan is being defined separately. Similarly, the WHHM needs for the use of finasteride for androgenetic alopecia in women will be defined in a separate SOI and a separate Marketing Needs Report.

This document defines the needs for a program to assure the most rapid registration possible. It also includes preliminary Phase V requirements that will need to be initiated quickly to assure the success of the product.

II. RECOMMENDATION

WHHM recommends the accelerated development of finasteride for the treatment and the prevention of androgenetic alopecia in men.

Based upon the assumptions presented in the attached SOI, worldwide third year sales for this indication are estimated to be $270 million, increasing to $580 million by the fifth year.

This forecast is dependent upon an accelerated development program leading to the WMA filing in 2Q'96.

The market for treatment and prevention of androgenetic alopecia is very much under-satisfied as far as medical treatments are concerned. Additionally, finasteride is assumed to be superior to minoxidil 2% which is currently the only FDA approved product. It is critical that the highest efficacy of finasteride for this indication is demonstrated in the Phase III clinical trials; it is also critical that the label does not include sexual adverse reactions and does not require the use of a condom. Therefore, WHHM recommends the development of the lowest dose that has the highest efficacy and best safety profile.

In addition, studies on efficacy and tolerability against the only currently approved prescription drug for this indication, minoxidil, will be needed at launch. Participation of opinion leaders in all these studies will be critical to the successful marketing of this product especially as this is a new therapeutic area for Merck. The identification of the opinion leaders should take place in conjunction with local Marketing groups to ensure that the appropriate opinion leader support will be available during filing and the launch phase.

III. DISCUSSION

A. Product Profile

The following initial product profile for finasteride in androgenetic alopecia in men is assumed:

1. Finasteride will be approved to increase hair growth and prevent further hair loss as demonstrated in the Phase III clinical trials.

2. Finasteride will demonstrate a significantly higher level of efficacy than the currently marketed minoxidil 2% for the treatment of the androgenetic alopecia and the prevention of hair loss. The efficacy of finasteride will be at least comparable to that of minoxidil 5% without compromising the safety of the product.

3. The dosage regimen will be one tablet of finasteride, once a day.

4. The safety profile of finasteride in androgenetic alopecia in men will be identical to the one experienced in the Phase II MPB trial. Therefore, we will be able to state that there was no difference in the clinical trials in the occurrence of sexual side-effects between the placebo and the finasteride treated group and we thus expect that there will be no requirement for the use of a condom. All other precautions and safety statements will be no stricter than the ones stated in the label for PROSCAR™.

5. Finasteride will result in superior patient satisfaction and quality of life compared to standard care and will be cost effective therapy compared to competitive products and procedures.

B. Preliminary Marketing Strategy

The preliminary marketing strategy for finasteride in androgenetic alopecia in men is to establish it as the first treatment for androgenetic alopecia that treats the underlying cause of the condition while being superior to existing treatments in terms of growing new hair, preventing hair loss, offering greater patient satisfaction and being more cost effective to the patient. The promotional efforts will target Dermatologists and GP's in addition to hairdressers and patients as this will be a "patient" driven product.

Promotionally, the following key points will be emphasized:

1. Finasteride grows new hair and prevents hair loss.

2. Finasteride treats the underlying cause of the condition through its unique mechanism of action.

3. Finasteride can be easily taken as one tablet, once a day.

4. Finasteride offers patient satisfaction and improvement in quality of life with minimal side effects.

C. Marketing Needs

1. Indication:

Finasteride should be indicated for the treatment of androgenetic alopecia in men to increase hair growth and prevent further hair loss.

The worldwide product circular for finasteride in androgenetic alopecia should not restrict its use to only those patients with vertex balding. We, therefore, need results of clinical trials which demonstrate efficacy in the temporal (frontal) balding area at the time of filing to avoid a restricted indication. This would further differentiate the efficacy and therapeutic benefits of finasteride from minoxidil.

2. Dosage/Administration/Formulations:

It is assumed that the dosage frequency for finasteride will be one tablet, once daily, to maximize our competitive position versus topical minoxidil.

As described in the Recommendation, WHHM supports the introduction of the lowest dose that has the highest efficacy with the best safety profile. However, if it is not possible to eliminate the safety concerns, use of condom and sexual adverse events, in the label inherited from PROSCAR™ , we support the introduction of the dosage with the highest efficacy that has a safety profile no worse than that of PROSCAR™. This last scenario will result in a lower sales forecast than the one submitted in the SOI.

If no dosage modifications are required for interactions with other drugs, food or for patients with renal impairment or liver disease this should be noted.

3. Clinical Pharmacology

The following objectives should be met in the clinical pharmacology program:

1. Studies should define the mechanism of action of finasteride in the treatment of androgenetic alopecia.

2. Studies should demonstrate safety and efficacy in young men aged 20-50.

4. Drug Interactions:

Marketing assumes that the drug interactions will be equivalent to the ones experienced with PROSCAR™. (See 2 above)

5. Precautions

Marketing assumes that the precautions to be taken will be similar to the ones stated in the label for PROSCAR™ with the exception of the requirement for use of a condom.

6. Adverse Reactions

Marketing assumes that the occurrence of sexual adverse effects will not be any different between the groups treated with finasteride and placebo.

Therefore, a statement similar to the following should be included in the prescribing information for finasteride:

> Finasteride is well tolerated; adverse reactions are mild when they occur and not any different from the patients in the placebo group.

7. Phase III Clinical Studies

It is important that the Phase III development program for finasteride, for use in androgenetic alopecia in men, assures the most rapid filing and registration possible. Therefore, studies to support the WMA/NDA filing should be designed to demonstrate that finasteride is a highly effective and well tolerated product for the treatment and prevention of androgenetic alopecia in men aged 20-50.

The studies should be designed to include sub-group analysis of patients of various age groups (20-30, 30-40, 40-50) as well as patients with different stages of the condition to show treatment of androgenetic alopecia and prevention of hair loss. The studies should be conducted in the US and in major international markets utilizing important opinion leaders. The results should be published in

recognized professional medical journals and presented at major medical meetings. Perhaps most importantly, the studies should highlight the importance of the satisfaction and improved quality of life of the patients with the treatment.

Therefore, the studies that should be included in the WMA/NDA are as follows:

- Two pivotal studies, one in the U.S. and one internationally, comparing finasteride vs placebo in young men (20-50 years) with Stage III or more (Hamilton Scale) androgenetic alopecia to show increased hair growth and prevention of further hair loss.

- Two studies, one in the U.S. and one internationally, comparing finasteride vs placebo in young men (20-50 years) with frontal balding (Stages I and II - Hamilton Scale) to show increased hair growth and prevention of further hair loss in balding areas other than the vertex.

- Studies to show the effect of finasteride on semen production in young men (20-50 years). These studies should also measure the time taken to reverse any effects seen. This will show a minimal effect on decrease of ejaculate volume of semen and that the effect is reversed within a short period of time when treatment is stopped.

- Studies to measure the vaginal absorption of finasteride from semen to increase the safety margin of exposure to finasteride. Currently, calculations of safety margin are based on 100% vaginal absorption of finasteride. If this is significantly lower this data would be valuable to support our position to delete the contraception section of the label.

As soon as possible after filing, results of the following studies should be available so that the initial indication can be broadened:

1. Long Term Use

   Long term clinical studies with finasteride should be continued for a sufficient length of time (3-5 years) to enable us to make promotional statements and label changes that efficacy (hair growth and delay or prevention of hair loss) is maintained over the long term and that no adverse effects peculiar to long term therapy exist. These data should be analyzed rapidly after each 12 month extension to support label changes and promotional activities.

2. Effect of finasteride on androgenetic alopecia in a broader patient population.

   Long term studies using finasteride for androgenetic alopecia in men above 50 years of age to determine efficacy and safety profile (if the dose is different from the 5mg in PROSCAR™).

All of the appropriate above named studies should evaluate patient satisfaction, quality of life and the general well-being of the patient using validated questionnaires and other appropriate methods.

D. Preliminary Phase V Studies

The following Phase V marketing studies should be initiated as quickly as possible and initial results should be available at the time of launch, to assure the success of finasteride for this indication:

1. Comparative studies with minoxidil to evaluate efficacy and safety.

   a. Short-term comparison
   Minoxidil 2% is the only prescription drug currently approved for the treatment of androgenetic alopecia. Upjohn is currently developing minoxidil 5% for the treatment of androgenetic alopecia and a registration package is expected to be filed in 4Q'94. This means that by the time of launch of finasteride, minoxidil 5% is expected to have been on the market for approximately 12 months. Based upon the information provided to us at the consultant's meetings, we expect finasteride to be superior in efficacy to minoxidil 2%, and equivalent in efficacy to minoxidil 5%.

   Marketing requires a study which would compare a combination of finasteride and minoxidil 5% with the individual components and placebo. This would measure hair growth, delay in hair loss and maintenance of effect while assessing patient satisfaction and quality of life. However, this marketing position will need to be revisited and reconfirmed once more information on the product profile of minoxidil 5% becomes available.

   b. Long-term comparison.
   Data show that the efficacy of minoxidil decreases after it has been used for approximately one year. A comparison study long enough to show the difference between the sustained efficacy of finasteride versus the waning effect of minoxidil 5% will be necessary to support our claim that finasteride treats the underlying cause of the disease. This study could potentially be an extension of the study described in D.1.a; however, both hair growth and delay in hair loss should be studied. The final design of this study will be dependent on the product profile of the minoxidil 5% strength.

2. Effect of finasteride on frontal balding.

   If the two frontal balding trials of the Phase III program do not show sufficient results to allow for a label change to support the use of finasteride on frontal balding, then further studies will need to be conducted with finasteride on the frontal areas. These studies should cover the effect of finasteride on re-growth of new hair as well as its effect on delay/decrease in hair loss in patients with androgenetic alopecia Stages I and II.