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Pfizer International

DATE: April 11, 1991

TO: Mr. William Heessels

FROM: Dr. Maria Guttadauria

SUBJECT: Sertraline Depression IRD

The sertraline depression IRD, broadly filed internationally September 1988, has received an unfavorable review in a number of countries. The common key issue is that regulators are not convinced of sertraline efficacy versus placebo. In the case of Sweden, Norway and The Netherlands, Central Research Sandwich prepared the best possible response based on available data, including new analyses of IRD data. In each case, the response was found to be unconvincing and the dossier was withdrawn. A similar Pfizer response has been filed in Australia, New Zealand and Colombia and we are awaiting their reaction. In France, regulators insisted that a placebo controlled, clomipramine comparative, inpatient study was required for approval. The dossier was withdrawn in France and the required study has been initiated by Sandwich. In Denmark, regulators also require a clomipramine comparative placebo controlled study and consequently the Danish queries remains unanswered. This week, we received comments from Germany which are similar to those of other countries.

In conjunction with Central Research Sandwich, strategies had been developed to address this situation. These were highly dependent on the availability of placebo controlled U.S. studies initiated post-NDA. However, preliminary analyses of these studies strongly indicate that they are not highly convincing of sertraline efficacy versus placebo and will not provide the strong database required to overcome regulatory obstacles. The reason for this appears to be a high placebo response, a problem known to be plaguing companies performing U.S. CNS trials. In the U.S., CNS studies are typically performed in centers devoted to performing these trials and which advertise for patients in print and TV media. Europeans view this practice as leading to the selection of an unrepresentative sample of "symptomatic volunteers" and the cause of the high placebo response seen in U.S. studies. Recently, due to the increasing number of trials being performed by the industry and the need to recruit greater numbers of patients for clinical trials, the placebo response rate seen in recently completed studies is even higher than the already high levels seen in the past ("placebo creep"). A high

placebo response makes it difficult to establish statistical differences between placebo and an effective active product.

At the present time, there are 4 studies which will be available in the near term for a second IRD (IRD2). These are listed with comments in the attached Table. As the comments indicate, there is considerable concern that these studies will not be convincing enough to gain approval. From a commercial point of view, the most critical countries are France and Germany. As shown in the attached table, these countries represent 25% and 13% of total 1990 International antidepressant sales respectively. Lack of approval in these countries will have devastating consequences on the commercial potential of sertraline internationally.

Recommendation

At present, there is only a modest chance that IRD2 as outlined above will be suitable given the regulatory challenges we face. A strongly positive, placebo controlled study is needed to ensure regulatory success. Therefore, we strongly recommend that a new placebo controlled study be initiated as soon as possible. To enhance the probability of success in a timely manner, we recommend that the study:

- be performed in Europe where "placebo creep" is not an issue and where European data is favored
- be designed to enhance the probability of success drawing on the knowledge gained from past trials
- be performed by Sandwich as a high priority to ensure GCP standards and timely completion.

Maria Guttadauria

MG:cmt

TOP TEN ANTIDEPRESSANT MARKETS
January - December 1990

Rank		$ Mill.	Trend	Share
1.	France	220.4	+ 29	25.1
2.	Germany	115.6	+ 8	13.2
3.	U.K.	86.5	+ 20	9.9
4.	Canada	77.0	+ 29	8.8
5.	Italy	65.8	+ 30	7.5
6.	Japan	60.7	+ 3	6.9
7.	Spain	39.8	+ 34	4.5
8.	Brazil	30.6	+ 96	3.5
9.	Netherlands	22.1	+ 26	2.5
10.	Belgium	16.6	+ 18	1.9
Total Top 10		735.0	+ 23	83.7
Total Int'l		$878.2	+ 23%	100.0%

Studies Available for IRD2

SPONSOR	STUDY	COMMENTS
CR	Double-blind versus clomipramine versus placebo (6 weeks)	Outcome uncertain because of inpatients and short study
NY	Double-blind versus fluoxetine (6 weeks)	Expect equivalent efficacy, not placebo controlled
UK	Double-blind versus dothiepin versus placebo (6 weeks) in primary care	Some differences from placebo seen for STL, but dothiepin equal to placebo
CAN	Double-blind versus imipramine (24 weeks)	Efficacy greater than that of imipramine, but high average dose of STL, not placebo controlled