SCHEHING AG

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Schering Aktiengesellschaft

Schering Chemicals Ltd. Medical Division Attr.

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Sammel-Nr.** (0311) 4591 Durchwahl (0311) 459Abt.: Med.Wiss.Ausl. 18orlin 65, Mullerstraße 170-172
Unasero Zeithen Dr. Fr/wy February 11,1969

Betreff

Re: Hormonal pregnancy tests

Dear Sirs,

Thank you for your memo of February 5th, 1969 with the attached correspondence with Dr. Künssberg and a provisional report on the retrospective study concerning hormonal pregnancy tests as produced by Mr. Dean.

Provided that the figures produced carry statistical significance at all, the results, in our opinion, are by no means alarming and in particular we do not see any basis for Mr. Dean's recommendation to withdraw Primodos from usage.

The main purpose of this investigation was to demonstrate or otherwise that hormonal pregnancy tests of the Primodostype had something to do with the observation of an increasing number of certain malformations. The figures presented show that there is no difference, in this respect, between untreated pregnancies and those during which a hormonal test was administered.

As far as the abortion rate is concerned, this in fact is increased in connection with Primodos against untreated pregnancies. However, such finding is indeed not as surprising as it may seem on first sight. Quite a number of those women who desire an early answer to the question on whether they are pregnant or not do so in the hope to be not pregnant and later-on may try all sorts of abortion inducing measures. An occasional one of these may be success-

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COMMITTEE ON SAFETY OF DRUGS Queen Anne's Mansions, Queen Anne's Gate, Lovine S.W.I.

Telephone: 01-839 9020 ext. 1327

ference:

In Confidence
Dear Dr.

7th August, 1969

I have recently had some discussions with Dr. Isabel Gal at Queen Charlotte's Hospital concerning her work on the possible teratogenicity of the hormone pregnancy diagnosis tests.

As a result of those discussions, I would like, on behalf of the Committee, to ask you to submit to us all the laboratory data on teratogenicity in animals, for your hormone pregnancy diagnosis tests ('Primodos') and also for your whole range of progestogens (e.g., 'Primolut') and oral contraceptive preparations.

With regard specifically to Primodos I would be grateful if you could also let us have estimates for the number of physicians' samples distributed to doctors. These should best be expressed as the annual total for the two tablet packs distributed in this way. It seems possible that a considerable number of women may have received treatment with physicians' samples and that our own estimates for the use of the presence test, based on National Health prescriptions, may provide substantial under-estimates of the actual number of women tested with this product.

Yours sincerely,

Sonior Medical Officer

Schering Chemicals Ltd., Victoria Way, Burgess Hill, Sussex. (52)

Although we have not become aware of adverse effects upon the embryo or foetus of an existing pregnancy, despite the embryo or foetus of an existing pregnancy, despite the embryo or foetus of an existing pregnancy, despite the embryo or foetus of primodos oral, we have decided exceptionally wide-spread use of Primodos oral for the early diagnosis to no longer recommend Primodos oral for the early diagnosis of pregnancy.

We furthermore request you to entirely cease the promotion of Primodos oral, effective immediately. The detailing of Primodos oral with the doctors, the mailing or distribution of samples not explicitly demanded spontaneously, as well as the dispatching or distribution of advertising material should be discontinued. Or distribution of advertising material should be discontinued. Please correspondingly revise your advertising schedule and advertising medium plan, and inform us about these alterations. The vertising medium plan, and inform us about these alterations. The Department Schriftliche Werbung shall no longer produce any Department for Primodos oral; orders previously issued will be material for Primodos oral; orders previously issued will be

It is your own responsibility whether or not you want to inform each particular doctor about the omission of the indication for early diagnosis of pregnancy, supplementary to those measures mentioned in the preceding paragraph.

We are convinced that you will not have to contend with significant short or medium-range sales losses, despite the cancellation of advertising and deletion of the indication for early diagnosis of pregnancy. In this connection, reference is especially directed at two important particulars:

1. The reservations made about Primodos oral concerning
the virilization risk, which cannot be excluded with
complete assurance, are not applicable to the Primodos
complete assurance, are not applicable to the Primodos
injection. The injectable form of Primodos can consecting
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injection of the injectable form of Primodos can consecting
and the consection of prescent also be recommended for the early diagnosis of presc

It would be gratifying if a shifting of "oral sales" to the injectable form could be attained as soon as possible. Please inform us on your own accord regarding your experiences on this topic.

2. The cancellation of the indication for early diagnosis of pregnancy is not a shot aimed by the FDA against our Primodos oral. It also affects the competitive preparations having a comparable composition.

It cannot be avoided that questions concerning the revised package enclosure will be directed at you in particular cases. We request you in such cases to observe the enclosed notification from the you in such cases to observe the enclosed notification from the Med.Wiss.Department as well as this letter. You are authorized to further direct the notification of the Med.Wiss.Department, in further direct the notification of the enquiring doctor. Please send particular cases of need, to the enquiring doctor. Please send continuing enquiries to Pharma Ausland for processing.

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PRIMODOS ORAL

The question concerning the value and safety of early diagnosis of pregnancy by using oral cestrogen-progestogen-combination preparations of the type Primodos oral has been repeatedly discussed during recent years. To date no scientific papers are indeed known, wherein a substantiated suspicion is papers are indeed known, wherein a substantiated suspicion is given for the virilisation or deformity of the roetus caused given for the virilisation or deformity of the roetus caused by the recommended dosage intake of a preparation possessing the composition of Primodos oral to diagnose an early pregnancy. The FDA also indicated only that no necessity exists for using such preparations in early diagnosis of pregnancy, since yet other methods of pregnancy diagnosis are available and side effects cannot be reliably excluded.

The Schering expert panel responsible for this area of enquiry dealt recently again with this problem and expressed the following opinion:

Primodos oral should no longer be recommended for the diagnosis of an early pregnancy. Despite the exceptionally widespread use of this preparation, there have specifically been no adverse effects occuring till now upon the embryo or foetus of an existing pregnancy. Since Primodos oral contains norethisterone existing pregnancy. Since Primodos oral contains norethisterone acetate, which nevertheless possesses an androgenic effect even acetate, which nevertheless possesses an androgenic effect even though extremely slight, this hormone should not be dispensed though extremely slight, this hormone should not be dispensed if a pregnancy exists and the dispensing occurs possibly in a critical phase of organ development.

As a hormonal method, the injection of Primodos is available for treatment. This injectable contains the natural hormones pestradiol (as pestradiol benzoate) and progesterone which are produced in greater quantities by the mother during pregnancy and possess a pregnancy maintaining effect."

Considering our "obligation for reliability", we have accordingly decided to cancel the indication "early diagnosis of pregnancy" for Primodos oral.

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