#1296

HALCION

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Ralph Nader, Founder

June 10, 1993

David Kessler, M.D., J.D.
Commissioner, Food And Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Kessler,

We have learned that the British (U.K.) Licensing Authority yesterday rejected an appeal by Upjohn and has finally revoked the license for Halcion, the widely-used sleeping pill which was temporarily suspended in the U.K. in September, 1991 because of an increased incidence of severe psychiatric adverse effects such as paranoia, depression, and memory loss. We have also obtained a copy of the July 17, 1992 letter from the U.K. Medicines Control Agency to Upjohn notifying the company that the government was proposing a permanent revocation of Halcion's license in the U.K. That letter states that : **"When the benefits [of Halcion] are considered in relation to the risks associated with the drug in normal conditions of use it is considered that the risk-benefit ratio is unacceptable. It is considered that there are other benzodiazepines available which have a lower frequency of psychiatric adverse effects and which are preferable on grounds of comparative safety."**

When we filed a petition with the FDA to ban Halcion from the U.S. market on July 22, 1992, we did not have a copy of the July 17, 1992 letter from the British government to Upjohn. It is quite clear from this letter, especially when taken in conjunction with an earlier December, 1991 letter from the British government's Committee on the Safety if Medicines (CSM) to the EEC explaining the reasons for a proposed permanent ban of the drug, why the British government took this action.

Upjohn's response to this final British action yesterday was that the company was "outraged". However, it is the American people who should be outraged that the Food and Drug Administration, by allowing this dangerous drug to stay on the market on this country, is failing to protect the hundreds of thousands of Americans who

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annually use this drug about which the British government has stated:

On this basis the CSM have concluded that triazolam [Halcion] is associated with an inadequate margin of safety in relation to dose and that the risks outweigh its benefits in relation to other benzodiazepines.

Considering all the information now available, it has been concluded that triazolam can no longer be regarded as safe for the purposes indicated in the licenses and that it should be withdrawn urgently from the market. It was considered that this warranted immediate suspension of the license. This action was authorized by UK ministers." (December, 1991 letter from British Committee on the Safety of Medicines to the EEC)

In Britain, the drug has gone through a complicated series of events over the 20 months since September, 1991 which are summarized below:

September 30, 1991 The Committee on the Safety of Medicines (CSM), an advisory group to the British Medicines Control Agency, the licensing authority for drugs in Britain, temporarily suspends sale of Halcion.

December 3, 1991 Upjohn appeals this decision to the CSM and its appeal is rejected. The CSM explains the basis for its action in a December, 1991 letter to the EEC, quoted above.

May 15, 1992 The Medicines Commission, another advisory group to the Licensing Authority, recommends that although the 0.25 milligram dosage form (one of the two on the market in the United States) is too dangerous and should be kept off the market, the 0.125 milligram dosage form can be used safely.

July 17, 1992 The Medicines Control Agency (MCA) acting on behalf of the Licensing Authority, rejects the advice of the Medicines Commission, instead concurring with the Committee on the Safety of Medicines and its own (MCA's) staff and writes to Upjohn, proposing a permanent ban on all dosage forms of Halcion.

February 1-4, 1993 Under the Medicines Act, Upjohn requests a private hearing in which the Licensing Authority appointed a person to hear presentations from the company.

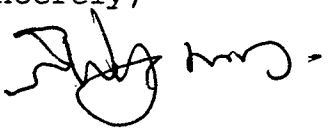
June 9, 1993 Upjohn announces that it has received a letter from the U.K. Licensing Authority rejecting the February appeal and revoking the license for all dosage forms of Halcion in the United Kingdom.

It is long overdue for the FDA to take this dangerous drug off the market. Millions of prescriptions have been filled and pills swallowed by unsuspecting Americans since the time the drug was taken off the British market. There is overwhelming evidence that Halcion is a dangerous drug that should never be used by anyone,

young or old, for any purpose.

As an FDA Commissioner pledged to protect the public from dangerous drugs and other FDA regulated products, your failure to act to ban Halcion is inexcusable. I look forward to a prompt response to this letter.

Sincerely,



Sidney M. Wolfe, M.D.
Director, Public Citizen's
Health Research Group

MEDICINES CONTROL AGENCY
Market Towers 1 Nine Elms Lane London SW8 5NQ
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From the Office of the Chief Executive

Mr J G Lee
Finance Director and Company Secretary
Upjohn Limited
Fleming Way
Crawley
West Sussex RH10 2NJ

KHJ/ab
17 July 1992

Dear Mr Lee

Halcion Tablets 0.25 mg - PL 0032/0058
Halcion Tablets 0.125 mg - PL 0032/0063
Triazolam Tablets 0.125 mg - PL 0032/0163.
Triazolam Tablets 0.25 mg - PL 0032/0164

I am writing to notify you of the Licensing Authority's determination of the matter of the proposed revocation of these licences following your hearing before the Medicines Commission. The Licensing Authority proposes that the licences for each of the products listed above shall be revoked.

Under paragraph 6 of Schedule 2 to the Medicines Act 1968 ("the Act"), the Licensing Authority proposes to determine the matter of the proposed revocation of the licences for the Halcion/Triazolam products in a way which differs from the advice of the Medicines Commission. In addition to the Medicines Commission report the Licensing Authority has had regard to your oral representations before the Commission and the Committee on Safety of Medicines (CSM) as recorded in the transcripts of proceedings, and all the written material which was before the Commission and the CSM.

A copy of the report of the Medicines Commission is attached to this letter. The report shows the Commission's findings and advice and the reasons for their advice. The Commission advised that licences for 0.25 mg products should be revoked and that licences for 0.125 mg products should be varied.

1. The grounds under the Act on which the Licensing Authority proposes that the licences be revoked are -

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1.1 that the matters stated in the applications on which the licences were granted were incomplete in a material particular (section 28(3)(a) of the Act) and

1.2 that products of the descriptions to which the licences relate can no longer be regarded as products which can safely be administered for the purposes indicated in the licences.

1.3 In applying these grounds, the Licensing Authority has had regard to Directive 65/65/EEC (in particular, Article 11) and has treated these grounds as meaning respectively -

(a) that the particulars supporting the application as provided for in Articles 4 and 4a are incorrect; and

(b) that the products prove to be harmful in normal conditions of use.

2. The reasons for the proposed revocation are as follows:

2.1 Reasons relating to the first ground -

2.1.1 Incomplete information on adverse effects and withdrawals from clinical trials was provided in the original product licence application in respect of Protocol 321 and withdrawals due to side-effects from comparative clinical trials.

2.1.2 Incomplete information from Protocol 321 was presented to the Committee on Safety of Medicines at a hearing in 1978 and was used to reassure the Committee on Safety of Medicines about the safety of triazolam in long-term usage.

2.1.3 The Licensing Authority considers that the submission of incomplete information referred to in paragraph 2.1.1 and 2.1.2 above is sufficient to justify revocation of the licences because the omitted information clearly supports concerns about the safety of the products (see 2.2 below). The absence of information by itself would not otherwise have been considered sufficient to justify revocation of the licences.

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2.2 Reasons related to the second ground -

2.2.1 The omitted information, which was eventually submitted to the Licensing Authority in 1991, shows that triazolam at doses of 0.5 and 1 mg causes frequent and disabling psychiatric adverse reactions. In Protocol 321, 47% of subjects given triazolam 1 mg experienced psychiatric reactions compared to 15% on placebo. In clinical trials of at least 28 days duration withdrawals from treatment due to psychiatric adverse reactions occurred in 9.9% of subjects on triazolam (0.5-0.6 mg), 1.9% on flurazepam (30 mg) and 0.8% on placebo.

2.2.2 If the available information had been presented completely and correctly, it is highly unlikely that product licences would have been granted. The Licensing Authority would have required extensive evidence to reassure them that lower doses do not produce significant psychiatric adverse effects. Therefore the acceptance of triazolam as safe at the licensed doses at that time must be regarded as flawed.

2.2.3 Post-marketing information obtained from spontaneous reporting schemes in the United Kingdom and United States of America, and published literature give cause for significant concern regarding the frequency of serious psychiatric adverse effects. Analysis of these data supports concern at all ages and all doses. In the UK 87% of 180 reports of psychiatric reactions occurred at the licensed doses. In the USA various psychiatric reactions have been reported 22-99 times more frequently with triazolam, mainly at doses of 0.25-0.5 mg, compared to temazepam, findings which cannot be accounted for by any known bias. The available epidemiological studies do not provide reassurance and do not adequately measure the frequency and severity of such effects.

2.2.4 The information now available shows that triazolam causes frequent and disabling psychiatric adverse reactions at doses of 0.5 and 1 mg when used in a population of young and middle-aged patients with no mental illness (see 2.2.1 above). These findings appear to have important implications for patients who are older or who have pre-existing mental illness, and who are treated with doses of 0.125-0.25 mg. They suggest that there is an insufficient margin

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of safety in relation to dose to safeguard patients against such reactions when the drug is used at the licensed doses in a general population. This concern is supported by the spontaneous reporting data referred to above (point 2.2.3).

2.2.5 The combined findings of clinical trials and post-marketing studies indicate that triazolam causes psychiatric adverse reactions at a greater frequency than other benzodiazepines. The increased risk of treatment with triazolam is related to dose and there is an inadequate margin of safety in relation to dose (see point 2.2.4). In the light of all the information now available, triazolam can no longer be regarded as safe. At the licensed doses, the risks of treatment are judged to outweigh the benefits to be obtained from its use.

2.2.6 The Licensing Authority has received advice from the CSM and the Medicines Commission that the 0.25 mg dosage form of triazolam is unsafe under normal conditions of use. Both advised that licences for 0.25 mg should be revoked, and the Licensing Authority, agreeing with the view of those bodies as to the safety of 0.25 mg triazolam products, proposes to accept that advice.

3. The reasons why the Licensing Authority does not propose to follow the advice of the Medicines Commission in respect of 0.125 mg triazolam products are as follows:

3.1 The Medicines Commission agreed with the Committee on Safety of Medicines (CSM) that the risks associated with triazolam at all doses when used in accordance with the current licence conditions outweigh any benefit to be obtained from its use. The Medicines Commission did not consider that the eight points raised by CSM had been resolved.

3.2 The Licensing Authority has received different advice from the CSM and from the Medicines Commission in respect of licences for 0.125 mg triazolam, although the advice is based on assessment of substantially the same evidence. Therefore the Licensing Authority has had to evaluate the reasons for the difference in order to reach a conclusion as to which course of action should be followed.

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3.3 From the report of the Medicines Commission it seems that the Commission recognised that there was a problem with the safety of triazolam but took a less serious view of it than the CSM. In assessing the risks associated with triazolam the Commission appears to have given different weight to certain factors and as a result has concluded that these risks are less than the Licensing Authority believes them to be. In particular:

(a) On the basis of spontaneous reporting in the UK the Commission stated that the adverse reactions with triazolam were similar to those reported for other benzodiazepines (point 2.3). However, the Licensing Authority considers that these data do provide a signal of an increased frequency of psychiatric adverse effects with triazolam compared to other benzodiazepines. In the UK 53% of psychiatric reactions reported occurred at a dose of 0.25 mg and 34% at a dose of 0.125 mg. One third of patients experiencing these reactions were aged 70 years or more. Furthermore, the US spontaneous reporting data provide even stronger support for the view that the frequency of psychiatric adverse effects is increased with triazolam (see 2.2.3 above). The Medicines Commission did not appear from their report to have attached any weight to these data.

(b) In their consideration of the phase II and III clinical trials the Commission concluded that the population of young and middle-aged patients with no mental illness did not appear to be particularly at risk (section 2.4). The Licensing Authority reaches a different conclusion from these trials. The phase II and III trials largely involved young and middle-aged patients with no mental illness. These trials demonstrated a clear increase in withdrawals from treatment due to side-effects compared with the comparator benzodiazepine.

(c) The Commission noted that most psychiatric reactions were neither life-threatening nor persistent, suggesting that they viewed many of them as non-serious. However, the Licensing Authority's view is that the nature of these reactions is such that they should be regarded as serious because of their potential for producing a major detrimental impact on patient's lives. The CSM also considered the psychiatric adverse effects of triazolam to be serious.

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(d) The Commission were unable to comment on the description of the adverse reactions to triazolam as frequent and disabling. The Licensing Authority view is that adverse reactions are frequent because in trials of at least 28 days duration 20% of patients withdrew due to side-effects compared to 10% on the comparator drug. These reactions are considered to be disabling because patients had to stop treatment as result. At doses of 0.5-0.6 mg psychiatric adverse effects were 5 times more common with triazolam compared to another benzodiazepine and 12 times more common as on placebo. These findings raise particular concern about the margin of safety for triazolam in relation to dose (see point 2.2.4).

3.4 The Commission advised that safety problems with the 0.125 mg triazolam preparation could be dealt with by action falling short of revocation of the licences. They advised that the licences should be varied in respect of the indication, dosage recommendations, duration of treatment, pack size and the inclusion of a statement promoting good sleep hygiene (section 4.2). This advice was based "on the understanding that 0.125 mg is efficacious in geriatric subjects and in a proportion of non-geriatric subjects". However, the Commission also noted that "a dose of 0.125 mg was efficacious in only a minority of non-geriatric subjects and that the efficacy of 0.25 mg was more convincing for these patients". Thus the restrictions recommended by the Commission would result in treatment of non-geriatric subjects being commenced at a dose which they regarded as efficacious in only a minority of such subjects.

3.5 The Licensing Authority agrees with the proposition underlying the Commission's advice that if the problems relating to triazolam could be dealt with by means falling short of revocation of the licences then they should be dealt with by such means. However, having evaluated the reasons for the difference in the advice received, the Licensing Authority considers that the variations proposed by the Commission would provide insufficient safeguards against the risks of treatment with triazolam even when it is used at the recommended doses and for no longer than the period recommended in the data sheet. Furthermore, it is well-established that benzodiazepines are sometimes used at higher doses and for longer periods than are recommended in data sheets and both these factors increase the risks associated with

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triazolam. This provides an additional reason for not dealing with the concerns by means of variations.

3.6 The view that the variations proposed by the Commission would be inadequate is based on consideration of both the risks and benefits of the 0.125 mg preparation. The Licensing Authority accepts the Commission advice that triazolam may have some advantage in respect of residual effects on performance but the overall benefits of the drug are limited by the modest efficacy in non-geriatric patients. When the benefits are considered in relation to the risks associated with the drug in normal conditions of use it is considered that the risk-benefit ratio is unacceptable. It is considered that there are other benzodiazepines available which have a lower frequency of psychiatric adverse effects and which are preferable on grounds of comparative safety.

4. In reaching its determination of the matter of the revocation of these product licences, the Licensing Authority has had regard for the CPMP Opinion on triazolam (Pharmacovigilance Opinion No. 11, dated 11 December 1991). The reasons for differing from the CPMP Opinion are given in sections 2.2.6 in respect of triazolam 0.25 mg products. In respect of 0.125 mg triazolam products the reasoning is based on the points made in sections 3.1 to 3.6 above.

Under paragraph 6 of Schedule 2 to the Act you have the opportunity, before the Licensing Authority determines the matter, to appear before, and be heard by, a person appointed for the purpose by the Licensing Authority, or of making representations in writing to the Licensing Authority, with respect to the Licensing Authority's proposal to determine the matter in a way which differs from the advice of the Medicines Commission. Please will you let me know within 14 days whether you wish either to appear before a person appointed or to make representations in writing.

Would you please acknowledge receipt of this letter.

Yours sincerely,

Kate Jones

Dr K Jones
Director and Chief Executive Medicines Control Agency
for and on behalf of the Licensing Authority