Public Citizen

NEWS RELEASE

HOLD FOR RELEASE UNTIL
Thursday, Sept. 2, 1993, 10:00 a.m.

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PUBLIC CITIZEN CALLS FOR BAN OF SANDOZ PRODUCT FOR TREATMENT OF POSTPARTUM BREAST ENGORGEMENT

WASHINGTON, D.C. -- Citing the agency's own four-year-old recommendations and descriptions of severely injured women, a consumer health organization today urged the U.S. Food and Drug Administration to immediately take steps to ban the prescription drug bromocriptine for the treatment of postpartum breast engorgement (PPBE).

The drug, marketed by Sandoz under the name Parlodel, is the subject of more than 220 adverse drug reaction (ADR) reports since 1989, when an FDA advisory committee recommended that it no longer be legally indicated or marketed for PPBE.

The reports include heart attacks, strokes, seizures and 13 deaths. More than 300,000 women each year -- 1.2 million since 1989 -- receive bromocriptine to suppress lactation and thus reduce postpartum breast engorgement, according to the consumer group, the Public Citizen Health Research Group.

Public Citizen also challenged the effectiveness of the drug. Prescribed to women who choose not to breastfeed, bromocriptine is intended to reduce the breast soreness, leaking and/or engorgement often experienced within 2-7 days postpartum. Without medication, the symptoms gradually resolve themselves two weeks after delivery.

[more]

Sufferers are treated effectively with breast binders, cold packs and over-the-counter pain medications.

Bromocriptine, however, merely postpones breast engorgement for a large number of women. Its side effects include marked blood pressure changes, dizziness, nausea, vomiting and occasional psychotic reactions.

The FDA moved in July 1989 to implement recommendations by its Fertility and Maternal Health Drugs Advisory Committee to withdraw Parlodel's indication for PPBE treatment. Unlike all other manufacturers of similar drugs, however, Sandoz replied that it must "respectfully decline" the FDA's request.

In a Sept. 2 letter to FDA Commissioner David Kessler, Public Citizen says Sandoz is "recklessly endangering the health of women."

"[The] FDA has inexcusably failed to assure that women are not given this unnecessary and potentially dangerous drug for PPBE," write Dr. Sidney Wolfe, M.D. and Dr. Stephen G. Moore, M.D., M.P.H., respectively the director and research associate of the Public Citizen Health Research Group. "Thus, annual sales of approximately $12.5 million for Parlodel to treat PPBE continue."

Public Citizen first petitioned the FDA in 1988 to revoke or amend new drug application approvals for all medications then being used for the treatment of PPBE.

Public Citizen's recommendations do not extend, however, to the indication of bromocriptine in a variety of conditions where it has been shown to be useful, including Parkinson's disease, acromegaly and hyperprolactinemic states.

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Ralph Nader, Founder

September 2, 1993

David Kessler, M.D., J.D.
Commissioner of Food, and Drugs
U. S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Kessler:

Four years ago, the FDA politely but ineffectively asked Sandoz to stop selling Parlodel (bromocriptine mesylate) for postpartum breast engorgement. We have learned that since then, over 1.2 million women have been given the drug, reflecting a combination of corporate greed - the wish to sell over $50 million worth of the drug instead of concern for the health of women who are particularly vulnerable to its life threatening adverse effects - and the FDA's bureaucratic paralysis.

Public Citizen's Health Research Group (HRG) urges the FDA to immediately take the necessary actions to assure that the prescription drug bromocriptine (Parlodel, Sandoz) is no longer legally indicated for the treatment of postpartum breast engorgement (PPBE) in women who choose not to breastfeed. The FDA's own Fertility and Maternal Health Drugs Advisory Committee made similar recommendations in June 1989, over four years ago, and the FDA then wrote to Sandoz asking it to voluntarily delete the PBBE indication (as all other companies making drugs for PBBE have done). Sandoz, recklessly endangering the health of women, refused in 1989 to stop promoting the drug for this indication, and the FDA has inexcusably failed to follow through, abdicating its responsibility to assure that women are not given this unnecessary and potentially dangerous drug for PPBE. Thus, annual sales of approximately $12.5 million for Parlodel to treat PBBE continue.[1]

We have obtained information from the FDA and elsewhere that indicates that more than 300,000 women each year continue to receive bromocriptine for PPBE. Since the 1989 committee recommendations were made to stop using bromocriptine for PBBE, the FDA has received over 220 bromocriptine related Adverse Drug

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Reaction (ADR) reports for women under fifty. These reports include descriptions of severe injuries, such as heart attacks, strokes, and seizures, and thirteen deaths related to bromocriptine use.

In response to this dangerous situation, Public Citizen's Health Research Group calls on the FDA to;

1. Immediately publish the notice of opportunity for hearing (NOOH) in the Federal Register to remove the indication for PBBE from the labelling for bromocriptine.

2. Promptly notify all physicians via the FDA Drug Bulletin that the FDA has started the process for withdrawing the indication.

Leading medical centers around the nation have already taken the initiative and prohibit the use of lactation suppressants within the medical practice of the institution. HRG forwarded a list of leading medical centers in which lactation suppressants are not used to the FDA documenting that lactation suppressants such as bromocriptine are not used in medical institutions such as Johns Hopkins, the University of North Carolina, Yale and Iowa.[2] The reasons cited by obstetricians at these institutions were that bromocriptine is expensive, ineffective (it merely postpones breast engorgement for a large number of women) and has been associated with such side effects as marked blood pressure changes, dizziness, nausea and vomiting and occasional psychotic reactions. The FDA should follow the example set by these institutions and remove the indication for the use of bromocriptine for PBBE.

Bromocriptine is appropriately indicated for the treatment of a variety of conditions, such as Parkinson's Disease, acromegaly and hyperprolactinemic states. HRG recognizes that Parlodel is useful for the treatment of these conditions, and therefore, HRG is not proposing a ban on Parlodel. HRG proposes only that the FDA change the indication so that Parlodel, with its risks of severe to fatal adverse effects, not be indicated for PBBE, a benign, self-limited condition.

Background

On November 29, 1988, Public Citizen's Health Research Group petitioned the FDA to revoke or amend the New Drug Application approvals for all medications then being used for the treatment of PBBE. Specifically, HRG petitioned the agency to revoke the New Drug Application approvals for Deladumone-OB, Deladumone and TACE, prescription drugs whose only indication was for PBBE. HRG further petitioned the FDA to amend the New Drug Application

approvals for bromocriptine and testosterone compounds to remove the indication for use for PBBE.[3]

On June 1 and 2, 1989, the Food and Drug Administration convened its Fertility and Maternal Health Drugs Advisory Committee to consider the benefits and risks of drugs used to prevent lactation and breast engorgement in postpartum women who do not breastfeed. The committee proposed that the indication be withdrawn for those drugs used for postpartum lactation suppression, including bromocriptine, estrogens, androgens, and estrogen-androgen combinations.

On July 13, 1989, Frank Young, M.D., Ph.D., Commissioner of the FDA, signed and approved of a memorandum written by his staff instructing the Director, Division of Metabolism and Endocrine Drug Products, FDA, to proceed with the implementation of the committee's recommendations.[4] The three-phase procedure was to include (1) meeting informally with drug sponsors requesting the withdrawal of the indication, (2) if companies refused, sending letters to sponsors again requesting the product be withdrawn, and (3) if companies continued to refuse, then publishing the FDA position in the medical literature, sending letters to physicians explaining the agency's position, and issuing a notice of opportunity for hearing (NOOH) in the Federal Register proposing that the indication be withdrawn.

After informal meetings (phase 1) failed, phase 2 of the above process was carried out on September 13, 1989, when the FDA wrote Sandoz requesting that the company voluntarily withdraw the indication for the use of bromocriptine for PBBE.[5] On October 25, 1989, Andrew Gustafson, Ph.D., Manager Regulatory Affairs, Sandoz Research Institute, wrote to the FDA in response and stated that Sandoz must "respectfully decline" to withdraw the indication.[6] All other producers of drugs used for treatment of PBBE voluntarily complied with the FDA's request, leaving bromocriptine as the only drug still "approved" by the FDA for the treatment of PBBE.

It is now September 1993, four years after the committee recommendations were made, but the NOOH has still not been published in the Federal Register. The indication for bromocriptine use for PPBE remains intact. Over the past four years well over one million women have received bromocriptine for PPBE. The FDA has received 220 reports of Adverse Drug Reactions associated with bromocriptine use in young women including many reports of severe injuries and thirteen reported deaths.

The Continued use of Bromocriptine in the Postpartum Patient

Dianne Kennedy, R.Ph., M.P.H, testified before the FDA's Fertility and Maternal Health Drugs Advisory Committee on June 1,

1989 and summarized the data on bromocriptine use.[7] The data indicated that, as of 1989, more than 1.3 million prescriptions for bromocriptine were being filled each year. Of those, approximately 36% were being prescribed by OB-GYN's, most if not all for treatment of PPBE. According to more recent NPA data, over 1.1 million prescriptions for bromocriptine were dispensed in 1992. There is no indication that the percentage prescribed by OB-GYN's has declined. The fact that prescribing patterns have not changed since the 1989 FDA recommendations is supported by sources within the FDA.

Therefore, it appears that more than 300,000 women continue to be exposed to the dangers of bromocriptine for postpartum lactation suppression each year. Since 1989, when the FDA requested that Sandoz voluntarily change the labeling of Parlodel, more than one million women have been exposed to bromocriptine for routine postpartum lactation suppression. There has been minimal if any decline in the use of bromocriptine for routine postpartum lactation suppression from 1989 to 1993.

Efficacy

The FDA's summary basis of approval for Parlodel, based on studies done before its approval, reported that between 18 to 40% of women who took the medication experienced some breast soreness, leaking and/or engorgement after the drug was stopped.

This is in contrast to women who neither breastfeed nor take lactation suppressing medications. Women in the non-medicated, non-breastfeeding group will begin lactation, which may be accompanied by breast pain and engorgement, within 2-7 days postpartum. The symptoms gradually resolve so that the majority of women are comfortable by two weeks after delivery. Postpartum women who do not breastfeed, and who do experience symptoms, can be treated with breast binders, cold packs and over the counter NSAIDs or acetaminophen for pain relief. Therefore, at the end of two weeks, most women who have not taken bromocriptine are symptom free while up to 40% of the women who have taken bromocriptine may now begin experiencing symptoms of breast discomfort.

Safety Concerns Before Approval

Bromocriptine use is associated with a significant number of both major and minor side effects. In the initial clinical trials described in the FDA's summary basis for approval, at least 23% of the women who took bromocriptine experienced at least one side effect. In women who took a daily dose of 5.0 mg per day, 28% had hypotension, 8.5% headache, 8.1% nausea, 7.4% dizziness, 0.7% fainting, 2.2% vomiting, and 2.5% rash. In addition to these minor side effects, a number of occurrences of severe to fatal

adverse drug reactions have been described in the medical literature and have also been reported to the FDA.

Current PDR Labelling and Recently Published Case Reports

The FDA approved labeling for bromocriptine in the 1993 Physicians' Desk Reference lists the following adverse drug reactions associated with bromocriptine use;

- symptomatic hypotension
- 50 cases of hypertension
- 38 cases of seizures - "occurring mostly in postpartum patients up to 14 days after initiation of treatment"
- 15 cases of stroke - "mostly in postpartum patients whose prenatal and obstetric course had been uncomplicated"
- four cases of acute myocardial infarction - "including three cases receiving Parlodel for the prevention of physiologic lactation" [8]

Because the 1993 PDR reports an identical number of adverse events as the 1989 PDR, it appears that the PDR has not been updated to reflect the increased number of reported severe patient injuries and deaths.

Case reports continue to be published in the medical literature detailing accounts of women who have been injured because of using bromocriptine for lactation suppression. Examples of these case reports are:

1. The article is a case report of a 32-year-old woman who experienced a myocardial infarction (heart attack) while using bromocriptine. The patient received a coronary angiogram five hours after the onset of symptoms which demonstrated a total occlusion of the mid-portion of the right coronary artery. The occlusion was opened with angioplasty.

   One month after being discharged from the hospital, the patient underwent a repeat angiogram two hours after oral bromocriptine challenge. The study showed a >70% narrowing of the right coronary artery. The authors concluded that the patient may have been experiencing bromocriptine induced vasospasm. The patient also experienced visual hallucinations and severe headache with bromocriptine use.[9] (published 1993)

2. Case report of a 19-year-old female who experienced new onset seizures, and hypertension four days postpartum and three days after starting bromocriptine. An MRI revealed a hemorrhage into the pituitary gland. The authors stated that the case illustrated a possible

association between the use of bromocriptine for PBBE and the onset of hypertension, seizures and intracranial hemorrhage.[10] (published 1991)

3. Case report of a 27-year-old woman with a prior history of pregnancy induced hypertension. The patient was started on bromocriptine two days after delivery. She presented with complaints of severe chest pain and headache ten days after delivery. At presentation she was noted to have a blood pressure of 180/120. The patient subsequently became unresponsive and developed a wide complex tachycardia. The patient was catheterized two months after the event and a 60-70% lesion of the mid-portion of the left anterior descending artery was noted. The authors concluded that bromocriptine may have triggered coronary spasm in this patient. The patient experienced a residual memory impairment and a partial receptive and expressive aphasia secondary to the event.[11] (published 1989)

There continue to be no studies, reported in the medical literature since 1989, which indicate that bromocriptine use is any more effective than alternative therapies such as breast support and non-steroidal therapy.

Adverse Drug Reactions Reported to the FDA

The Adverse Drug Reaction (ADR) reports filed with the FDA between August 1979 and May 1993 illustrate the fact that women have been and continue to be injured and killed by using bromocriptine. There have been 726 ADR's filed with the FDA in the above mentioned time period for women under the age of fifty. Thirty-two of the reports are for patient deaths.

In June 1989, the FDA's Fertility and Maternal Drugs Advisory Committee unanimously recommended that lactation suppressants not be used by women as a component of routine postpartum care. Since those recommendations were released, an additional 220 bromocriptine related ADR's have been filed for women under fifty, most, if not all of whom, were probably prescribed the drug for the treatment of PBBE. The ADR's reported since June 1989, include a variety of adverse events related to bromocriptine use including 13 patient deaths, 68 patient hospitalizations, and at least 14 disabling injuries.

The majority of the thirteen patient deaths reported since June 1989 were related to either central nervous system (CNS) events or cardiovascular (CV) events. The causes of death for the thirteen patients can be categorized as follows; 1. CNS, which included five patient deaths from causes such as stroke and seizures, 2. CV, which included two patient deaths, 3.

hypertension, which was the primary diagnosis in at least one patient death, 4. unknown, a category which included two reports of patient deaths in which no further information was available in the ADR reports, and 5. other, which included deaths from diverse causes such as one case of a death related to a pulmonary embolus.

In addition to the deaths, there have also been multiple reports of serious injuries occurring in women receiving bromocriptine for postpartum lactation suppression which have resulted in hospitalization or permanent disability. Representatives of HRG testified at the June 2, 1989 FDA advisory committee hearings that, based on FDA ADR reports as of August 1988, there had been eight reported cases of myocardial infarctions, ten reports of strokes, and 29 reports of seizures. Since that testimony was given, there have been approximately an additional ten patients with myocardial infarctions, eleven patients with strokes, and 42 reported patients with seizure episodes.

The ADR's have been submitted by physicians in 46 states, the District of Columbia, and ten foreign countries. The only states not reporting bromocriptine ADR's were Alaska, Delaware, Hawaii, Idaho, and New Hampshire.

Sandoz Response: Selling As Much Parlodel For PBBE For As Long As It Can: Misleading Doctors

Sandoz has a strong economic incentive for continuing the promotion of Parlodel use in postpartum patients. Assuming that approximately 36% of the approximately 1.1 million annual Parlodel prescriptions are for use in postpartum patients, then this is an approximately $12.5 million annual market for Sandoz.[12]

Sandoz has a well established history of being slow to respond to FDA regulatory requests. For example, in August 1983 the FDA instructed Sandoz to change the labelling for Parlodel, but the changes were not implemented until December 1984.

A second example occurred in February 1987. The FDA requested that Sandoz list uncontrolled hypertension as a contraindication for the use of the drug and to report the increasing number of hypertensive crises, strokes, and myocardial infarctions which occurred subsequent to the 1984 labeling change. The FDA also required Sandoz to send a Dear Doctor letter to OB-GYN physicians informing them of the labelling changes.

The Dear Doctor letter was sent in August 1987, but a subsequent follow up letter was required, due to concern that many physicians had not received the Dear Doctor letter. Prior to the Dear Doctor letter, a letter was sent from Sandoz Pharmaceuticals

to the Sandoz field representatives referring to the labeling changes, which stated , "[R]emember, this issue [the labeling change reporting the increasing number of heart attacks, strokes and hypertensive crises] should not be mentioned unless a discussion is initiated by the physician." (emphasis in original)[13]

A third example of Sandoz' unwillingness to cooperate is the fact that the company refused to voluntarily change the indication for the drug. Sandoz argued that the use of a lactation suppressant should be a personal choice between a woman and her physician.[14] Sandoz further stated:

> Because we believe that Parlodel continues to be safe and effective for its labeled indication, and that there is no basis for withdrawal of the NDA under § 505(e) of the Federal Food, Drug and Cosmetic Act, we respectfully decline to withdrawal the indication at this time.[15]

Sandoz has repeatedly demonstrated that it is not willing to voluntarily change the labeled indication for the use of Parlodel for PPBE. The corporation has displayed a consistent pattern of delay and resistance to FDA oversight. Therefore, the FDA must take action to require Sandoz to comply with the directives outlined in the June 1989 memorandum signed by Commissioner Young.

Conclusion

Public Citizen's Health Research Group has long opposed the routine use of bromocriptine in the postpartum patient. HRG has maintained that; 1. postpartum breast engorgement (PPBE) is an inconvenience, but it is not a serious disorder, 2. bromocriptine has not been shown to be more effective than other more conservative treatment methods in the treatment of PPBE, 3. bromocriptine has rare but potentially fatal side effects in some women. Therefore, the risks of bromocriptine use far outweigh the benefits.

The FDA's Fertility and Maternal Health Drugs Advisory Committee agreed with HRG's position and requested the withdrawal of the indication in 1989. Four years later bromocriptine is still being used for PPBE. The FDA has failed to follow through with its own procedural outline as described in the memorandum to the Commissioner, dated June 27, 1989.

HRG calls on the FDA to complete the indication change process begun four years ago. The FDA should immediately publish the NOOH in the Federal Register and notify all physicians of the indication change via the FDA Drug Bulletin. This action must be taken now to prevent any more women from being killed or

otherwise harmed by this unnecessary medication.

Sincerely,

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

Stephen G. Moore, M.D., M.P.H.
Research Associate

References

1. Number of prescriptions based on an estimated 36% of 1.1 million annual Parlodel prescriptions being used for PBBE. Dose of 2.5 mg twice a day for 14 days assumed for calculation. Price per pill of $1.13 calculated by averaging the 30-count price as published in Drug Topics Red Book: Annual Pharmacists' Reference 1990, 1991, and 1992.

2. Letter from D. Teich, MD, S. Wolfe, MD, Public Citizen's Health Research Group to Frank Young, MD, PhD, Commissioner, FDA, dated March 15, 1989.

3. Citizen Petition, Petitioners: Public Citizen's Health Research Group, National Women's Health Network to Frank Young, MD, PhD, Commissioner, Food and Drug Administration, dated November 29, 1988.

4. Memorandum, from S. Sobel, MD, Director, Division of Metabolism and Endocrine Drug Products, to F. Young, MD, PhD, Commissioner, FDA, dated June 27, 1989.

5. Personal communication, Letter form Solomon Sobel, MD, Director, Division of Metabolism and Endocrine Drug Products, Center for Drug Evaluation and Research to Andrew Gustafson, PhD, Manager Regulatory Affairs Sandoz Research Institute East Hanover, New Jersey, dated September 13, 1989.

6. Personal communication. Letter from Andrew Gustafson, Ph.D., Manager, Regulatory Affairs, Sandoz Research Institute to Solomon Sobel, MD, Director Division of Metabolism and Endocrine Drug Products, Office of Drug Evaluation. dated October 25, 1989.

7. Testimony by Dianne L. Kennedy, RPh, MPH, Drug use for lactation suppression. Before the Fertility and Maternal Health Drugs Advisory Committee, June 1, 1989.

8. Physicians' Desk Reference, 47th edition, 1993, pg. 2116.

9. Larrazet F, et al. Possible bromocriptine-induced myocardial infarction. Annals of Internal Medicine 1993;118:199-200.

10. Gittleman D. Bromocriptine associated with postpartum hypertension, seizures, and pituitary hemorrhage. General Hospital Psychiatry 1991;13:278-280.

11. Ruch A. Postpartum myocardial infarction in a patient receiving bromocriptine. Obstet Gynecol 1989;74:448-451.

12. Supra see note 1.

13. Personal Communication from Sandoz Pharmaceuticals - Lou Santora, Executive Director of Sales, Harold Feldman, MD, Associate Director Clinical Development and Janice Diorio, Parlodel SBU Manager to Sandoz Sales Representatives, Hospital Representatives, Area Hospital Managers, Sandoz Regional Managers, and Sandoz Area Sales Managers, dated August 20, 1987.

14. Supra see note 6.

15. Id at 2.