

From The Chief Medical Officer:
Dr Henrietta Campbell CB

Castle Buildings
Upper Newtownards Road
Belfast BT4 3SJ

Telephone: 028 90 520563
Fax: 028 90 520574

E-Mail: henrietta.campbell@dhsspsni.gov.uk

HSS(MD)5/02

22 March 2002

To: All General Practitioners (for cascade to practice nurses)
Medical Directors of HSS Trusts (for cascade to consultant surgeons,
consultants in palliative medicine and other professionals, as appropriate)
Lead Cancer Clinicians in Cancer Units
Directors of Public Health in HSS Boards
Community Pharmacists
Prescribing Advisers in HSS Boards
Primary Care Medical Advisers in HSS Boards
Directors of Nursing in HSS Boards and Trusts
Directors of Pharmacy in HSS Boards and Trusts
Chief Executives of HSS Trusts
Northern Ireland Cancer Registry
Northern Ireland Hospice

Dear Colleague

TAMOXIFEN AND RISKS OF THROMBOEMBOLIC EVENTS

Initial findings from an international study on the use of tamoxifen in preventing breast cancer confirmed that tamoxifen can prevent breast cancer in healthy women at high risk of the disease. The results so far show that incidence was reduced by one-third, compared to women taking a placebo. The study also indicated, however, that tamoxifen can increase the risk of thromboembolism, particularly during and immediately after major surgery or periods of immobility. A copy of the press release outlining the preliminary results of the study is attached.

Tamoxifen is already a widely used and inexpensive hormonal treatment for women following treatment for both early and advanced breast cancer. Breast cancer is a major source of morbidity and mortality, with approximately 900 new cases and 300 deaths each year in Northern Ireland. About 50-65% of cases ("oestrogen-receptor positive") are potentially suitable for hormonal treatment. Hormones have two potential uses: in early disease, as adjuvant therapy to surgery, radiotherapy or treatment with cytotoxic (cell-killing) drugs, to delay the recurrence of the disease; and in advanced (metastatic) disease, to prolong survival and reduce the effect of symptoms.

We know that the benefits for women being treated for breast cancer with tamoxifen manifestly outweigh any risks. This is the licensed use of tamoxifen. It is important that women taking the drug as a treatment continue to do so as there is overwhelming evidence that tamoxifen saves lives among women with breast

cancer. Women should be aware of the symptoms of venous thromboembolism, and if they have any sudden onset of breathlessness they should consult their doctor immediately.

The study being reported concerns preventing cancer in healthy women at high risk of breast cancer. This is not a use of tamoxifen that has yet been licensed except in the context of a trial. It is important that a full analysis of this and other trials is made to consider whether the benefits of the preventative action outweigh potential risks.

Summary of key messages:

for women who have had breast cancer and who are suitable for tamoxifen treatment – there is clear evidence that the benefits for women being treated for breast cancer with tamoxifen have been shown to outweigh the risks. This is the licensed use of tamoxifen. It is important that women taking the drug as a treatment continue to do so as there is overwhelming evidence that tamoxifen saves lives among women with breast cancer. They should be aware of the symptoms of venous thromboembolism, and if they have any sudden onset of breathlessness they should consult their doctor immediately.

for women in this trial – preliminary results indicate early evidence of benefit in preventing breast cancer in women at high risk, but there is also evidence of some increase in risk from thromboembolism, especially during and immediately after major surgery or periods of immobility. Advice on this was given to women participating in the trial and they should also be aware of symptoms of thromboembolic events and seek medical advice if concerned. A letter has been sent to each of the 7,000 women in the trial by the study co-ordinators recommending that the study should continue without change.

Further information can be obtained from MCA Information Line 020 7273 0000.

Yours sincerely

HENRIETTA CAMPBELL (DR)
Chief Medical Officer

PRESS RELEASE

First IBIS results show tamoxifen reduces breast cancer in healthy high-risk women – but still too early to know if benefits outweigh risks

First results from the long-awaited IBIS trialⁱ into the use of tamoxifen to prevent breast cancer in healthy women at high risk have firmly established that the drug can indeed cut the incidence of the disease.

These preliminary results were presented today (Wednesday 20 March) at the 3rd European Breast Cancer Conference in Barcelona together with an overview of the four breast cancer prevention trialsⁱⁱ. Results from the previous studies have been mixed.

In addition, nine trials using tamoxifen for treatment of breast cancer patients and who were therefore at high risk of developing a second cancer in the opposite breast, were also reviewed.

IBIS lead investigator Professor Jack Cuzick, who is from Cancer Research UK, told the conference that the incidence of breast cancer was reduced by a third in the women taking tamoxifen in the IBIS trial with 68 cases of breast cancer compared with 101 among those taking the placebo. When the results of all the prevention trials were combined the overall reduction was 38%. The trials of the adjuvant treatment of breast cancer in patients showed a slightly greater (46%) reduction in the incidence of second cancers in the opposite breast.

The reduction in incidence of breast cancer in IBIS was found only in oestrogen receptor positive (hormone positive) breast cancers with no effect on cancers that were oestrogen receptor negative. The benefit was the same whatever the age of the woman, whatever the level of risk and whether or not she was taking hormone replacement therapy.

However, while the benefits of tamoxifen for treating breast cancer patients are indisputable, there is still no conclusive answer as to whether the benefits outweigh the side effects for prevention in healthy women, according to Professor Cuzick. “All along the line, we have kept the volunteers in the trial fully informed of developments. That is why we and the Independent Data Monitoring Committee felt it was right to report these preliminary findings at this point. But, I stress that these results are preliminary and it is essential to continue to follow the participants to see if a particular high risk group of healthy high-risk women can be identified for whom the benefits of tamoxifen clearly outweigh any risks.”

It is also too early, he said, to judge the ultimate effect on breast cancer deaths among the prevention trials in healthy women. In the IBIS trial only four breast cancer deaths have been reported so far – two in the tamoxifen arm and two in the placebo arm. However, the likely potential mortality benefit could be calculated if certain factorsⁱⁱⁱ were assumed. “For high risk women, we calculate that deaths from breast cancer within 10 years of diagnosis would be reduced by 18%.”

Other key findings from IBIS were also generally in line with the other tamoxifen trials, confirming that there was a 2 to 3-fold increase in the risk of endometrial cancer and a 2 to 3-fold increase in the risk of thromboembolism for women taking tamoxifen.

For all of the prevention trials combined there was no effect on all-cause mortality with 112 deaths in the tamoxifen arms and 122 in the placebo arms. However, there were variations, with statistically non-significant reductions in death in two trials, no difference in one trial and a statistically significant excess of deaths in the IBIS trial.

Professor Cuzick said: “In IBIS there were more deaths in the tamoxifen arm with 25 against 10 in the placebo arm. Deaths from cancers other than the breast were higher, but the numbers of these cancers were not increased, suggesting this was likely to be a chance finding. Also, with the exception of venous

thromboembolic events, other vascular and cardiac events were not increased. This suggests that, apart from two possible deaths from pulmonary embolism (PE), the increases in other vascular and cardiac deaths were also chance findings.

Professor Cuzick said that in the prevention trials overall, non breast cancer deaths appeared to be similar, but the small excess of PE deaths in IBIS and one other trial – the American P1 study– indicated that thromboembolism was the most important complication of tamoxifen use.

“Every effort should be made to reduce this risk, although we must keep it in perspective. It is about the same level of risk as that faced by a woman taking HRT, and if you are a breast cancer patient taking tamoxifen for treatment it is absolutely essential that you continue the treatment. Tamoxifen is a lifesaver and the single most effective medical treatment for breast cancer. Any risks from tamoxifen used for treatment are far outweighed by the benefits. There are many more thousands of breast cancer patients alive today because of tamoxifen.”

Professor Cuzick concluded: “We need, however, to be aware of the potential risks of blood clots in women taking tamoxifen. We know that there is a link between blood clots and surgery, with 40% of all the clotting events in our trial occurring within three months of surgery or following immobility. Most of these events were in the tamoxifen arm. Thus, it would seem a wise precaution to discontinue tamoxifen before any major surgery, to ensure that appropriate anti-clotting treatments are provided during surgery and not to recommence tamoxifen until at least one month after surgery. Similar precautions would also be appropriate for women who become immobile for any reason.”

Abstract no: 20

ⁱ The International Breast Cancer Intervention Study (IBIS) involves more than 7,000 healthy women at increased risk of breast cancer. Half are taking the drug tamoxifen and half are taking a placebo (dummy) tablet. It is a randomised double-blind trial i.e. one in which neither the volunteers nor the doctors know which women are taking tamoxifen or placebo. It is coordinated by the British charity Cancer Research UK and the countries taking part are the UK, Finland, Switzerland, Belgium and Australia and New Zealand through the ANZ Breast Cancer Trials Group.

ⁱⁱ The three other prevention trials are:

- NSABP P1 Tamoxifen Prevention Trial (USA)
- The Royal Marsden Hospital chemoprevention trial
- The Italian National Trial

ⁱⁱⁱ The assumptions when estimating the potential effect on breast cancer mortality were:

- an incidence rate of 6/1000 breast cancer per year
- 25% of the breast cancers would be ER negative
- tamoxifen reduces the incidence of ER positive cancers by 50% for five years and 30% in the next five years
- tamoxifen is ineffective for ER negative cancers
- 10 year survival for ER positive cancers in the placebo arm is 75%
- 10 year survival for ER positive cancers in the tamoxifen arm is 70%
- 10 year survival for ER negative tumours is 60%.