UK licence for cisapride suspended

Annabel Ferriman *BMJ*

The product licence for cisapride (Prepulsid), a drug used to treat gastric and digestive disorders in adults and children, has been suspended by the Medicines Control Agency after five deaths in the United Kingdom and 125 deaths worldwide that are thought to be associated with the drug.

When the Committee on Safety of Medicines recently reviewed the drug, which is made by Janssen-Cilag, it found rare but serious disturbances in heart rhythm associated with it.

Since 1988, when cisapride was licensed in the United Kingdom, the yellow card scheme—under which doctors report adverse drug reactions—has received 60 reports of serious cardiovascular reactions, five of which were fatal.

Worldwide there have been 386 reports of serious ventricular arrhythmias (125 of which were fatal) suspected to be due to cisapride and 50 reports of sudden unexplained death. Risk factors predisposing a patient taking cisapride to heart rhythm disturbances, such as interacting medicines, could be identified in many but not all cases.

In February the US Food and Drug Administration warned doctors that the drug should be used only as a last resort, for patients with the worst cases of gastro-oesophageal reflux disease when other treatments have failed (5 February, p 336). In July Janssen-Cilag suspended marketing of the drug in the United States, but cisapride is still available there through a limited access programme for patients who can show it is of "unique benefit."

Last week the Department of Health told patients to stop taking the drug and see their doctors over the next few weeks to discuss their treatment. "Stopping cisapride does not carry any risk," the advice said.

Concern about cardiac arrhythmias has recently led to a Europe-wide review of the risks and benefits of cisapride, which will consider what indications for the drug, if any, are justified. The suspension of UK licences will be reassessed once the review has been completed in 2001.

Professor Alasdair Breckenridge, chairman of the Committee on Safety of Medicines, said: "We have concluded that at the present time the balance of risks and benefits for cisapride is not favourable. There are several alternatives to cisapride available."

Health minister Lord Philip Hunt said: "The independent scientific advice of the Committee

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The mayor of New York, Rudolph Giuliani, explains what steps the city is taking to control mosquitoes carrying the West Nile virus, which killed seven people in New York state last year. Central Park was closed earlier this week while it was sprayed with pesticides, after mosquitoes carrying the virus were detected there. Helicopters were also expected to spray the areas of Queens, Brooklyn, and Staten Island. The disease, which spreads from birds to humans through mosquitoes, had not been seen in the United States before last year, earlier outbreaks having been confined to Uganda, Israel, Romania, and South Africa (*BMJ* 1999;319:941).

on Safety of Medicines means that measures short of suspending cisapride marketing authorisations are not adequate to protect UK public health, which is of course our priority."

Marketing of cisapride has also been suspended in Germany and Canada.

A spokesman for Janssen-Cilag UK said that serious

cardiovascular adverse effects occurred principally in cases where the drug had been used "with contraindicated medicines or in patients with contraindicated comorbidities."

"Janssen-Cilag continues to believe that Prepulsid can be used with an acceptable benefit to risk ratio in appropriate patients." □

Cancer drug may cause heart failure

Scott Gottlieb *New York*

A team of researchers is calling for long term studies investigating the risk of heart failure among women taking the breast cancer drug trastuzumab (Herceptin) as a result of new evidence that the drug might precipitate heart failure, especially in women with underlying cardiovascular problems.

Trastuzumab is a monoclonal antibody that binds to a protein found on the surface of some cells. The protein, HER2, helps to regulate cell growth. By binding to tumour cells, trastuzumab inhibits the growth of cancerous cells. It is currently

approved for the use in metastatic breast cancer.

In an editorial in *Circulation* (2000;102:272-4), lead author Dr Arthur Feldman, director of the Cardiovascular Institute at the University of Pittsburgh Medical Center in Pennsylvania, and colleagues said that trastuzumab should not be given to any woman who has any prior problem with the heart muscle. That would include women with high blood pressure or a high cholesterol level.

They noted that heart failure occurs in 7% of women taking trastuzumab alone, and the rate

jumps to 28% in women taking the drug alongside other chemotherapy drugs.

As a result, extending the use of trastuzumab to women whose breast cancer has not spread or metastasised seems irresponsible in view of the troublesome side effects on the heart, according to Dr Feldman and colleagues.

In May the biotechnology company Genentech, the drug's manufacturer, issued a letter to doctors alerting them that the deaths of 15 women with advanced metastatic breast cancer had been linked to the use of trastuzumab.

The Food and Drug Administration (FDA) said at that time that trastuzumab is "still a very safe drug" despite the reports of the 15 deaths. The administration said that the deaths were

among patients with allergic or infusion reactions or respiratory problems, or a combination of those events, and not with cardiovascular complications.

Dr Feldman said he believed that fear of cancer, and particularly fear of breast cancer, was combining to cloud clinical judgment: "I think the most interesting thing is that if someone were to go to the FDA with a new drug for heart failure or cholesterol or high blood pressure—all of which are leading killers of people—and that drug was associated with even a 1% incidence of cancer, it would never be approved by the FDA."

"No manufacturer would take the drug to the FDA. Yet here is an anticancer drug that is associated with a 28% incidence of heart failure and it is approved." □