Dutch GPs warned against new contraceptive pill

Tony Sheldon *Utrecht*

Dutch GPs are being advised by their own professional body not to prescribe a new low dose, monophasic oral contraceptive, marketed under the trade name Yasmin, until studies have established whether it is as safe as other contraceptive pills.

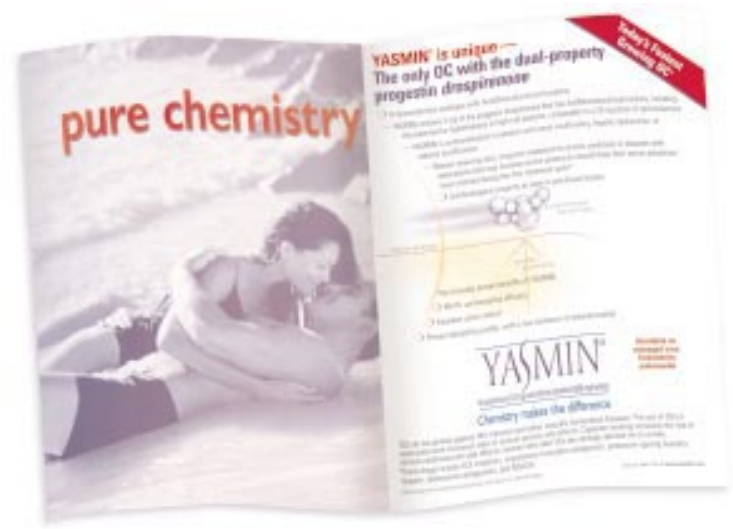
The new contraceptive, which is a combination of drospirenone (a progestogen) and ethinylestradiol, has been available in several European countries since 2000 and was approved by the US Food and Drug Administration last May. It is licensed for use in the United Kingdom, where it is being launched next week.

Last year a 17 year old Dutch girl who had been taking Yasmin died from a venous thrombosis. Although no direct link with Yasmin has ever been shown, 40 cases of venous thrombosis among women taking Yasmin, two of which were fatal, have now been reported in Europe.

The Dutch College of General Practitioners has now reiterated its position that GPs should continue to choose the second generation pill, because of the lack of epidemiological data on the risk of thrombosis from Yasmin.

The Dutch Medicines Evaluation Agency, which has a leading role in the European Union in assessing the safety of Yasmin, has as a result of the two deaths asked that the drug carry a warning that the risk of venous thrombosis from using it remains unknown. Before licensing Yasmin the agency had also asked for more research into side effects and coagulation. Final results from a comparative study over three years involving 3000 women have yet to be published.

The agency said: "The impression exists that GPs are inclined to prescribe the new pill earlier in the assumption that the risk of venous thrombosis is smaller than with the second and third generation of contraceptive pill," but added that this cannot be concluded from the available data.



Speaking on a Dutch radio station, Frits Rosendaal, professor of clinical epidemiology at Leiden University Medical Centre, called for GPs not to prescribe Yasmin until the risk of venous thrombosis was known.

He said: "I am not satisfied it is absolutely safe." He was alarmed that as many as 40 cases have been reported voluntarily by doctors so soon after Yasmin was registered. "Doctors seem to believe it is safer, but we don't know. We are making the same mistake as with the third generation contraceptive pill."

Yasmin's manufacturer, the German pharmaceutical company Schering, is "absolutely convinced of the safety of Yasmin." It has written to all Dutch GPs, gynaecologists, and pharmacists, saying that the 40 reported cases of venous thrombosis among a million users of Yasmin, mainly in Europe, do "absolutely not indicate an increased risk of venous thrombosis."

A Schering senior medical adviser, Dr Egbert Klaassen, said the company had conducted all the necessary research acceptable to the Medicines Evaluation Agency and the FDA. Interim results from Schering's post-marketing surveillance study of a million cycles show that, after one year, one venous thrombosis occurred among Yasmin users, compared with five among users of other oral contraceptives.

Yasmin has been licensed in Europe since November 2000. Schering estimates that about 35 000 women are using it in the Netherlands and 500 000 throughout 17 countries in Europe. □

Arthritis drug should be removed from market, says consumer group

Fred Charatan *Florida*

In a petition last month to the Food and Drug Administration, Public Citizen, a Washington based consumer watchdog, asked that leflunomide (Arava) be removed from the market.

Leflunomide was first marketed in the United States in September 1998 to treat rheumatoid arthritis. Over the next three years, it was associated with at least 130 cases of severe liver toxicity, including 56 admissions to hospital and 12 deaths, according to FDA data. Two of those who died were in their 20s.

"To have this many deaths and severe reactions over such a short time is truly disturbing," said Dr Sidney Wolfe, director of Public Citizen's Health Research Group, which submitted the petition to the FDA.

"When there are other treatments that are more effective and don't endanger patients as much as this drug, there is absolutely no reason for the FDA to keep Arava on the market."

In a comparison between leflunomide and methotrexate, which is an equally or more effective drug for treatment of rheumatoid arthritis, Public Citizen found that over the three years it has been on the market, leflunomide was linked to six times more cases of fatal liver toxicity and 13 times more reports of hypertension than methotrexate, although 6.8 million (5.5 times) more prescriptions were filled for methotrexate than for leflunomide during that time. Also, leflunomide has been associated with 12 cases of Stevens-Johnson syndrome, and methotrexate with none.

Another danger of leflunomide is that it remains in the body for an extremely long time. Warnings already on its packaging suggest that byproducts could remain in the body for months, so that even if patients stopped the drug after an adverse reaction started, the damage could continue to affect patients for months.

Public Citizen's petition is supported by Dr David Yocum, director of the Arizona Arthritis Center at Arizona Health Sciences Center, who recently ended a tenure as chairman of the FDA's arthritis drugs advisory committee. Dr Yocum said that he agrees the drug should be withdrawn from the market.

After similar serious reactions to leflunomide in Europe, the European Agency for the Evaluation of Medicinal Products issued an urgent warning last year to patients and doctors about the drug's toxicity.

"Before it was approved by the FDA there was evidence that leflunomide led to liver complications, and now the dangers are even clearer," Dr Wolfe said. "No more patients should be subjected to these risks." □