COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

STATEMENT ON FURTHER TOXICITY STUDIES IN THE RAT OF A HYDROGEL FILLER FOR BREAST IMPLANTS

Introduction

1 During 2000, because of concerns raised by clinicians about the safety of the fillers used in breast implants, the Medical Devices Agency (MDA) had decided to review the safety data on all breast implant fillers available in the UK. These included a hydrogel pre-filled breast implant manufactured by Poly Implant Prostheses. In September 2000, at the request of the MDA, the Committee considered a submission questioning the significance of the findings in a 90-day toxicity study in rats implanted with this hydrogel. The product was voluntarily withdrawn from the UK market in December 2000 and an MDA Device Alert was issued to advise plastic surgeons and implanted women. MDA indicated that further advice on the safety of these implants would be provided as soon as it became available.

2 COT considered additional data in February 2002 and concluded (COT Statement COT/02/1 - March 2002) :

i. The Committee considered that the conclusion of the new study, namely that there were no pathological findings in the organs examined, was not supported by the limited experimental results provided. There were limitations in the design of the study, the interpretation of its findings and the report was considered to be imprecise and inadequate.

ii. The Committee agreed that the findings from the original and new studies could not be discounted. The Committee was not able to exclude the possibility that the reported lesions were indicative of a toxic or immunologically-mediated response.

iii. The Committee considered that the new studies provided no further information to permit clarification of the extent or significance of toxicological risks.

iv. The Committee repeated its previous conclusion that further testing should be undertaken including the administration of single doses of the filler gel with longer-term follow-up. The Committee stressed the

need for the design and reporting of further studies to be compatible with current guidelines for chronic toxicity tests.

The implant

3 The hydrogel filler originally comprised 92% of physiological saline gelled with 8% of a polysaccharide. This filling material has subsequently been modified and the saline replaced by a buffer. It is understood that the polysaccharide is based on a cellulose derivative that forms long, linear chains linked by bridges. This gel is contained within a silicone elastomer shell.

Degradation of the filling material

4 Limited data were provided previously on the potential for *in vivo* degradation of the filling materials (both buffered and unbuffered). A substantial proportion of the material dosed to animals was not recovered and the fate of this material had not been ascertained. No additional information has been provided. Therefore we still consider that the potential degradation of the hydrogel had not been adequately addressed.

The new rat toxicity studies

5 The manufacturer had provided results from a 2-year subcutaneous carcinogenicity study and a 1-year implantation study, intended to address the concerns raised by COT in relation to the earlier studies.

6 In the 2-year study, groups of fifty female Wistar Han rats were injected in each flank subcutaneously with 1/60 of their body weight of the modified gel filler material divided between two sites or with saline as a control. Groups of dosed and control rats were killed after 24 months. Limited observations were made during life with detailed examinations at necropsy. In addition haematology and biochemistry were evaluated in sub-groups of 20 implanted and control animals at 12, 18 and 24 months, biochemistry was assessed on all animals at 24 months. Urinalysis was performed on sub-groups of 10 implanted and control animals at 18 and 24 months. A more extensive range of organs was examined histopathologically than in the earlier studies.

7 In the 1-year study, groups of fifteen male and fifteen female Sprague-Dawley rats were injected in each flank subcutaneously with 1/60 of their body weight of the modified gel filler material divided between two sites or with saline as a control. Limited observations were made during life with detailed examinations at necropsy. In addition haematology and biochemistry were evaluated in sub-groups of 10 implanted and control animals per sex at 3, 6 and 12 months, biochemistry was assessed on all animals at 12 months. Urinalysis was performed on sub-groups of 10 implanted and control animals

per sex at 3 and 6 months and all animals at 12 months. An extensive range of organs was examined macroscopically with a more limited range examined histopathologically.

8 The glomeruli of the kidneys of the animals in the test group of the 2-year study were significantly dilated compared to those of the controls and the test group showed significantly higher incidences of tubular nephropathy, sometimes associated with interstitial nephritis. Changes in creatinine levels in serum were observed in the first twelve months of the 2-year study but these these were no longer evident after 24 months. Diuresis, excretion of urinary proteins and creatine clearance were similar to control values at the end of the study. The dilatation of the glomeruli of the kidney was associated with the presence of what was thought to be test material contained in macrophages.

Evaluation of the findings

9 The previously observed effects in the liver, kidney and lymph nodes in the earlier inadequately designed and reported studies of shorter duration were not confirmed in these new studies and hence should no longer be considered as indicative of a toxic effect. The changes in creatinine level indicated a functional effect in the first twelve months of the study, but by 24 months no difference was apparent although there was substantial variability between animals at this time. As a result, any difference was not statistically significant, but there may still have been a biologically significant effect. However due to the limited urinalysis for kidney function in the studies, it was difficult to determine if significant damage to the kidneys was occurring.

10 Any effect in the kidney could have been the result of a combination of factors in individual animals rather than representing a functional toxic effect of the hydrogel. We concluded that the marginal effects seen in the kidney were most likely a treatment related effect but not clearly adverse. We noted that, compared to most other species, older rats are very susceptible to interstitial nephritis, especially in studies of longer duration.

11 We noted that exposure to the Hydrogel in the new studies was intended to represent a worst case situation. In women generally the amount is likely to be lower and duration of exposure is likely to be limited, however similar exposure on a body weight basis could occur in women following simultaneous rupture of both implants.

12 We were informed that the ongoing rate of rupture for all breast implants is 1-5% per annum. When rupture is detected (usually by change of volume), the implants are usually removed and replaced. Therefore, we considered that exposure to Hydrogel would, in most cases, be for a relatively short period of time. We recognised that so-called ‘silent’ ruptures, where leakage may take time to become

apparent, could result in longer exposure times. Although we recognise that there is additional uncertainty, we considered Hydrogel unlikely to have acute toxic effects.

13 We were concerned that there seemed to be minimal follow-up to monitor kidney function in women with these implants, and that continued surgeon-patient contact was limited. We were informed that the Independent Review Group on Silicone Gel Breast Implants had previously expressed similar concerns over inadequate follow-up. Women with implants are often reluctant to attend for follow-up consultations and therefore there had been increased provision of information to patients on possible adverse events after surgery.

Conclusions

14 We conclude that the results of the two studies provide reassurance that the effects previously noted in the liver, kidney and lymph nodes were not indicative of a toxic effect.

15 We conclude that the marginal effects seen in the kidney in the new studies were most likely a treatment related effect but not clearly adverse. Taking account of the susceptibility of older rats to kidney effects, especially in longer studies, we considered that similar effects would be unlikely to occur in humans.

16 The exposure of rats to the Hydrogel in the new studies was generally greater in amount and duration than that occurring in women following rupture of their implants. We conclude that the results of these studies when considered together with the existing data, suggest that subcutaneous exposure to the Hydrogel would not lead to toxic effects in women with these implants.

17 We recognise that removal of the implants is a clinical decision which would need to be based on all relevant medical factors, including the risks associated with removal of the implants.

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