

**Australian Government****Department of Health and Ageing**
Therapeutic Goods Administration

File Reference 2011/016208

Attention: [REDACTED]

Eska Australia
Unit 32 A&B of 2-6 Chaplin Drive
LANE COVE NSW 2066
Australia

Dear [REDACTED]

Proposal to cancel the entry of a medical device from the Australian Register of Therapeutic Goods under Section 41GN of the Therapeutic Goods Act.

Device Name: Eska Bionik Resurfacing Hip Implant
ARTG Number - Name: 118430 - Eska Australia - Prosthesis, internal, joint, hip, resurfacing
Sponsor: Eska Australia
Manufacturer: Eska Implants GmbH and Co

1. As a delegate of the Secretary to the Department of Health and Ageing for the purposes of Section 41GN of the Therapeutic Goods Act 1989 (the Act), I am writing to inform you that I propose to cancel the entry of the Eska Bionik Resurfacing Hip Implant (the Device) from the Australian Register of Therapeutic Goods (the Register).

Decision

2. I am proposing to cancel the entry of the Device because I am satisfied that its safety and performance are unacceptable.

Background

3. The TGA has reviewed orthopaedic implants that were identified in the 2010 Annual Report of the Australian National Joint Replacement Registry (NJRR) as having higher than expected revision rates. The annual reports of the NJRR and detailed information about implants that were identified as having higher than expected revision rates are available at <http://www.dmac.adelaide.edu.au/aoanjrr/publications.jsp>
4. The Device was one of the implants identified in the Report as having higher than expected revision rates (Text, Tables and Diagrams in pages 147-152 of the Report).
5. On 29 September 2010, the TGA wrote to Eska Australia about the fact that the Device had been identified in the NJRR report. The TGA letter included a comprehensive Implant Analysis Report from the NJRR about the performance of the Device in Australia and asked questions about complaint and adverse event reports, clinical trial results and

other clinical evidence and for a statement from Eska Australia or the manufacturer in relation to any benefits afforded by the use of the Device that may compensate for the seemingly higher revision rates. The TGA received a response from Eska Australia on 29 October 2010.

6. The NJRR Implant Analysis Report for the Device, the complete response from Eska Australia and a case summary prepared by the TGA were presented to the Orthopaedic Expert Working Group (OEWG) for consideration at a meeting that took place on 24 November 2010. The OEWG is a group of orthopaedic surgeons, nominated by the Australian Orthopaedic Association, who advise the TGA on matters relating to the safety and performance of orthopaedic implants.
7. The OEWG expressed concern about the high revision rates being experienced with the Device in Australia and advised that Eska Australia had not made a convincing argument in favour of the safety and performance of the Device. On 17 January 2011, the TGA notified Eska Australia about the advice of the OEWG and that the TGA would have to make a decision about the ongoing availability of the Device in Australia. The letter also advised Eska Australia to review their previous submission and resubmit. The TGA received a further submission from the manufacturer of the Devices – Orthodynamics – on 25 February 2011.
8. As part of its review of the new information, the TGA sought further advice from the OEWG. The OEWG considered all of the available information about the Device, including the Orthodynamics submission mentioned in 7 above once again at a meeting that took place on 25 May 2011. The submission from Orthodynamics failed to abate the OEWG's concern about the revision rates associated with the use of the Device.
9. After considering the information before me including the advice provided by the OEWG, I am satisfied that the safety and performance of the Eska Bionik Resurfacing Hip Implant are unacceptable and propose to cancel the product from the Australian Register of Therapeutic Goods.

Legislative Overview

10. Under Subsection 41GN(1)(e) of the Therapeutic Goods Act, the Secretary of the Department of Health and Aging has the power to cancel the entry of a medical device from the Register if she is satisfied that the safety or performance of the medical device is unacceptable.
11. Before cancelling the medical device from the Register, the Secretary must inform the person in relation to whom the medical device is included in the Register (the Sponsor) that she proposes the cancellation, setting out the reasons for it; and give the Sponsor reasonable opportunity to make submissions in relation to the proposed cancellation.

Material Considered

12. In coming to my decision I have considered the following material:
 - a. Section 41GN of the Therapeutic Goods Act 1989 (see **Attachment A**).
 - b. The 2010 Annual Report of the Australian National Joint Replacement Registry (NJRR)
 - c. The detailed individual implant report dated September 2010 from the NJRR regarding the safety and performance of the Device that was provided to you under cover of the letter dated 29 September 2010.

- 151
- d. A detailed individual report dated September 2011 from the NJRR regarding the safety and performance of the Device (This report can be downloaded from <http://www.dmac.adelaide.edu.au/aoanjrr/publications.jsp>);
 - e. A letter from the TGA to Eska Australia dated 29 September 2010, and Eska Australia's response dated 29 October 2010;
 - f. The advice of the OEWG following their meeting of 24 November 2010 where they considered the NJRR Implant Analysis Report for the Device, the complete response from Eska Australia and a case summary prepared by the TGA;
 - g. A letter from the TGA to Eska Australia dated 17 January 2011 advising Eska of the OEWG's recommendations and seeking further information; and the response to that letter provided by Orthodynamics GmbH on 25 February 2011.
 - h. The further advice of the OEWG after they considered the Orthodynamics response mentioned in (g) above at a meeting that took place on 25 May 2011.
 - i. The 2011 annual report of the NJRR and the associated detailed implant analysis from the NJRR about the ESKA Bionik resurfacing implant.

Findings in relation to facts

13. The 2010 Annual Report of the NJRR identifies the Device as an implant that is experiencing higher than anticipated rates of revision. In 2010 the revision rate for the device was 2.75 revisions per 100 observed years. At that time the revision rate of similar implants in Australia was 0.98 revisions per 100 observed years. Compared to the average performance of all other similar implants used in Australia the adjusted hazard ratio for the Device is 2.31. This means that the Device is 2.31 times more likely to need revision than similar prostheses. This finding is statistically significant at the 0.13% level. Therefore, I find that the revision rate of the device is significantly higher than that of other implants of the same type and that the corresponding increased risk of revision for patients who receive the Device over those who receive a similar prosthesis is unacceptably high. This is a concern because revision surgery is associated with significant morbidity and mortality.
14. The safety and performance of the Device has deteriorated significantly since the 2010 NJRR report. The detailed implant performance report from the NJRR compiled in September 2011 indicates that the revision rate for the Device is now 3.64 revisions per 100 observed years, and that the hazard ratio is 3.48 (this finding is statistically significant at 0.1% level)
15. The cumulative revision rate for the Device is rising steadily and the rate of revisions for the Device relative to the rate of revisions for all other similar devices (the hazard ratio) is also increasing with time. The proportion of revisions due to loosening/lysis, pain and implant breakage is much higher than the proportion of revisions for similar reasons in similar implants. The implant is being used in several hospitals in several states, and the number of revisions appears to be related to the number of implants used at a particular site. This would indicate that surgical technique is not playing a significant role in the revision rate. Therefore, I find that the difference in risk of revision between the Device and similar implants increases with time since original implantation and that the pattern of usage does not explain the seemingly poor performance of the Device in Australia.
16. The approach used in your response dated 29 October 2010 was to explain, on a case by case basis why the implants have been revised, and then to provide citations of published literature that suggests that the Device has had good results elsewhere in the world. You have claimed that all of the revisions in the "Type of Revision" table that were provided to you by the TGA on 29 September 2010 were due to trauma, surgical error or inexperience.

One of the revisions is said to have been on a ceramic on ceramic implant and the remaining 8 were metal on metal. In your response all of these are dismissed as not being implant related:

The revision of the ceramic on ceramic implant is claimed to be due to a femur fracture due to AVM.

Of the remaining revisions, you have claimed that 3 were due to neck of femur fractures (2 of which are claimed to be due to trauma), 3 revisions are due to malposition of the acetabular cup and in two cases the femoral heads were not in the varus position.

17. Your response of 29 October 2010 does not provide any supporting evidence (eg a cross reference to investigation reports, implant retrieval analysis etc) for the assertion that none of the revisions are due to implant failure. Also your response does not completely account for all revisions and is not consistent with the NJRR data. For example the NJRR data cites 3 fractures, not 4. You have also stated that the femoral neck fractures are not related to implant failure. We believe this type of failure to be related to the Device because preservation of the femoral neck is part of the design philosophy of this type of implant. Well designed resurfacing implants should minimise femoral neck fracture as far as possible. For the reasons given in paragraph 15 I do not believe that surgical technique is responsible for the high revision rates attributed to the use of the Device.
18. In the response dated 29 October 2010 ESKA also provided some published papers and abstracts about the performance of the ESKA implant. Paragraphs 19-22 highlight some critical aspects of some of the citations provided by ESKA in that response.
19. In a general article about hip joint surface replacement Rudert et al report a case series of 20 Bionik surface replacement prostheses inserted between 2003 and 2005. At an average follow up period of 18 months there were no infections or aseptic loosening, but there was one femoral neck fracture and one dislocation, placing the revision rate at approximately 10% (or $(100 \times 2 \text{ revisions} / 1.5 \text{ years} \times 20 \text{ implants} = \mathbf{6.6 \text{ revisions/100 component years}})$).
20. In the "Data Summary" on the series involving 248 patients (number of implants not stated, but we assume one implant per patient), enrolments began in February 2003 and patients were followed until February 2006 (estimated average follow up of 1.5 years). During that time ESKA reports that there were 7 revisions for various reasons - mostly femoral neck fracture. The revision rate is not calculated, but based on the information provided above, an estimate would be $100 \times 7 \text{ revisions} / 1.5 \text{ years} \times 248 \text{ implants} = \mathbf{1.88 \text{ revisions/100 component years}}$.
21. Beaulé et al report a retrospective review of 94 cases for which the mean follow up was 4.2 years. 13 patients are reported to have had a bad outcome. A bad outcome is defined as conversion to Total Hip Replacement (THR), radiolucency of greater than 1mm or narrowing of the femoral neck by greater than 10%. It is not clear whether all 13 required revision, but if they did then the revision rate was **3.29 revisions/100 component years**.
22. I find that a careful reading of the literature provided by ESKA on 29 October 2010 reveals that the experience outside Australia is as bad or worse than that which is being reported by the Australian National Joint Replacement Registry.
23. The submission from Orthodynamics dated 25 February 2011 makes the following points:
 - a. Cera-Metal implants experienced 11.11 revisions per 100 component years. This high revision rate may have skewed the revision rate for all Bionik implants and has now been discontinued.

- b. The Bionik Resurfacing Heads have undergone a design change in 2008. It is expected that the revision rates will improve.
 - c. The revision rates in Tasmania have been very high and may have skewed the revision rate.
 - d. The clinical studies conducted abroad suggest very good performance.
 - e. Further laboratory testing is being conducted on the effect of "Biosurf" on femoral component wear rates.
24. At their meeting on 25 May 2011 the OEWG noted that there have been a number of iterations of the design of the femoral head and that Orthodynamics is expecting that the most recent design is satisfactory. They also noted the Tasmanian revisions. However, as the registry does not indicate the user of the device, it cannot be determined whether they were repeat revisions for the same surgeon. The Group was also of the view that even if the most recent design is better, the data indicates that there is still a higher risk of revisions than for other similar devices. Overall members of the OEWG agreed that the design changes have not improved the device and confirmed their previous advice.
25. Your submission dated 25 February 2010 cites two studies conducted by Gerdesmeyer and one study conducted by Rudert. The study by Rudert reports a revision rate of 10%. The Gerdesmeyer study on the minimally invasive approach is too small and the follow up time too short to be able to make any meaningful comparisons on revision rates with the NJRR. The more extensive study by Gerdesmeyer seems to be reporting a similar revision rate to that being reported for resurfacing hip implants (of any sort) in Australia. I have already outlined in paragraphs 19-21 that the revisions being reported in the literature that you provided with your response of 29 October 2010 appears to be as high if not higher than that being reported by the NJRR. Therefore, I am not convinced by the claim made in page 7 your submission of 25 February 2010 that the "clinical literature does not match the conclusions of the NJRR"
26. In the submission you also indicated that:
- "The UK National Joint Registry reports a resurfacing revision rate of 6.2% at five years. The NJRR data shows that the Bionik resurfacing head has a revision rate of 5.1%. the revision rate is not excessive for resurfacing devices, as demonstrated by the UK National Joint Registry Data"*

The comparison that you have made is not valid for two reasons:

1 - The 6.2% revision rate for resurfacing implants is the **Cumulative Percent Revision** for resurfacing implants in the UK at 5 years. The 5.1% revision rate that you have quoted in your submission is not the Cumulative Percent Revision for the Device referred to in the 2010 UK NJR report. The UK NJR reports do not include the Bionik implants in their analysis.

2- The Cumulative Percent Revision figures in the UK cannot be directly compared to those in Australia because surgeons in the UK are using different indicators for revision - for example, elevated Co/Cr blood levels are being used as an indication for revision of Metal on Metal Implants in the UK. The Cumulative Percent Revision for resurfacing implants in Australia is 3.1% at 3 years and 4.6% at 5 years.

The NJRR has not yet calculated the Cumulative Percent Revision for the Device at five years, but at 3 years that figure is 10.0% - almost 3 times higher than the same revision rate measure for all other resurfacing hip implants.

27. You have also indicated that the Device was introduced into the market on the basis of a successful hip simulator wear test in 2003, and that concerns over additional test results obtained in 2007 led to improvements in the Device. Unimproved product continued to be supplied in Australia, but your submission does not make clear when the supply of old stock ceased in Australia. The last paragraph in page 7 implies that this occurred recently but the fifth paragraph of page 7 implies that it occurred in 2008. Whichever the case may have been, I note that the latest report from the NJRR indicates that of the 114 Bionik resurfacing prostheses implanted in Australia between January 2007 and December 2010, 7 have been revised, so the revision rate has continued to be high even after the introduction of improvements to the Device. Therefore I am not able to confirm that "the NJRR is reporting lower revision rates".
28. The tests conducted in 2003 do not appear to have predicted the relatively poor performance of the Device, and there are significant questions on the ability of laboratory testing to predict the performance of metal on metal implants in particular. Also, there appears to be no clinical evidence to demonstrate that the improvement in polishing in the Biosurf components will significantly improve the performance of the Device. Therefore I do not have reliable evidence before me that suggests that the revision rate of the implant will improve, but I do have reliable evidence that suggests that the revision rate of the implant is unacceptable and may continue to increase.
29. As a result of the facts outlined in paragraphs 13-28 above I am satisfied that:
- The revision rate of the Device is unacceptably high and continues to be high even after corrective actions said to have been undertaken by the manufacturer.
 - Eska Australia and Orthodynamics were provided with sufficient time and opportunity to make submissions in relation to the revision rate of the Device, both in relation to the revision rate itself and in relation to unique design features that may compensate for the higher risk of revision.
 - Having considered information from the Sponsor of the Device in Australia and the Manufacturer as well as advice from the OEWG, the benefits of continued supply of the Device do not outweigh the risks associated with the higher than expected revision rates.
 - Since revision surgery is associated with considerable morbidity and a low but not insignificant mortality rate, the high rate of revision of the Device indicates that both the performance and the safety of the implant are unacceptable.

Reasons for decision

30. Section 41GN(1)(e) of the Act provides the Secretary of the Department of Health and Ageing the authority to cancel the entry of a medical device from the Australian Register of Therapeutic Goods if "the Secretary is satisfied that the safety or performance of the kind of device is unacceptable".
31. As outlined in paragraph 20 of this letter, I am satisfied that the safety and performance of the Device are not acceptable, and therefore Section 41GN(1)(e) applies.

Conclusion

32. I am proposing to cancel the entry of the Device from the Australian Register of Therapeutic Goods because, for the reasons set out in paragraphs 13-26 of this letter, I am satisfied that the safety and performance of this implant are unacceptable.

33. I am issuing this notice of intention to cancel in accordance with the provisions in Section 41GN (2) and 41GN(3) of the Act which stipulate that, before cancelling the entry of a medical device under Section 41GN, the Secretary must inform the Sponsor in writing about the proposal to cancel and set out the reasons for it. The Secretary must also give the Sponsor a reasonable opportunity to make submissions in relation to the proposed cancellation.

Actions Required

34. You now have an opportunity to make a further submission in relation to this proposal to cancel the entry of the Device in the ARTG.
35. If you wish to make a submission in relation to this proposal to cancel I request that you do so **in writing** and submit it **within 20 working days of the date of this letter** to:

Dr Jorge Garcia
 Director, Biomaterials and Engineering Section
 Therapeutic Goods Administration
 PO Box 100, Woden, ACT 2606
 e-mail: jorge.garcia@tga.gov.au
 Telephone : +61 2 6232 8432

36. I believe that the 20 working day deadline is reasonable because Eska Australia and the manufacturer were provided the opportunity to make submissions in relation to the implant on two previous occasions. I also wish to stress that your previous submissions have already been given careful consideration by the TGA and the Orthopaedic Expert Working Group. Therefore any further submission should provide new evidence and/or highlight facts that you believe have been overlooked or misinterpreted. It is not necessary to repeat your previous submissions.

Date of effect

37. The cancellation will NOT take effect until any submission that you wish to make in relation to this proposal has been considered. If the TGA does not receive a submission within 20 working days of the date of this letter, then the TGA may consider moving to cancel the Device from the Register.

Other Matters

38. If you require further information regarding this matter, please contact Dr Garcia on the telephone or e-mail provided in paragraph 35.

Yours sincerely



Head, Monitoring and Compliance Group
 Therapeutic Goods Administration
 (Delegate of the Secretary to the Department of Health and Ageing for the purposes of Section 41GN of the Therapeutic Goods Act 1989)

Date: 14/11/2011

ATTACHMENT A

41GN Cancellation of entries of kinds of medical devices from the Register after notice of proposed cancellation

- (1) The Secretary may, by written notice given to the person in relation to whom a kind of medical device is included in the Register, cancel the entry of the kind of device from the Register if:
 - (a) medical devices that were devices of that kind when the kind of device was included in the Register have changed so those medical devices are no longer devices of that kind; or
 - (b) the person in relation to whom the kind of medical device is included in the Register refuses or fails to comply with a condition to which that inclusion is subject; or
 - (c) the Secretary gives to the person a notice under section 41JA:
 - (i) that requires the person to give to the Secretary information or documents relating to the kind of device; and
 - (ii) in respect of which section 41GM does not apply;and the person fails to comply with that notice within a further 10 working days from the day specified in that notice; or
 - (d) the person contravenes subsection 41MP(1) or 41MPA(1) in relation to the kind of device; or
 - (e) the Secretary is satisfied that the safety or performance of the kind of device is unacceptable; or
 - (f) the Secretary is satisfied that any certification, or part of a certification, under section 41FD in relation to the application for inclusion of the kind of device in the Register is incorrect, or is no longer correct, in a material particular.

Note: The matters that must be certified under section 41FD include compliance with the essential principles and the application of conformity assessment procedures, being able to substantiate the compliance and application, and compliance with advertising requirements.
- (2) However, before cancelling the entry of the kind of device from the Register, the Secretary must:
 - (a) inform the person in writing that the Secretary proposes the cancellation and set out the reasons for it; and
 - (b) give the person a reasonable opportunity to make submissions to the Secretary in relation to the proposed cancellation.
- (3) The Secretary is not to make a decision relating to the proposed cancellation until the Secretary has had regard to any submissions the person makes under paragraph (2)(b).

41GO Limiting cancellation of entries from Register to some medical devices of a particular kind

- (1) If the Secretary is satisfied that the ground for cancelling the entry of a kind of medical device from the Register applies only to some medical devices of that kind, the Secretary must limit the cancellation to the medical devices to which that ground or any other ground for cancellation applies.
- (2) If the cancellation of the entry of a kind of medical device from the Register is limited to some medical devices of that kind, the Secretary:
 - (a) must vary the entry in the Register accordingly; and
 - (b) must not delete the entry from the Register because of the cancellation.

41GP Publication of cancellation of entry from Register

The Secretary must cause to be published in the Gazette, as soon as practicable after cancelling an entry from the Register of a kind of medical device, or of some devices of a particular kind, a notice setting out particulars of the cancellation.

41GQ Date of effect of cancellation of entries from Register

If the Secretary cancels an entry of a kind of medical device, or some devices of a particular kind, from the Register, the cancellation has effect:

- (a) if the cancellation is under section 41GK or 41GL—on the day on which the notice of cancellation is given to the person in relation to whom the kind of device was included in the Register; or
- (b) in any other case—on such later day as is specified in the notice, being a day not earlier than 20 working days after the notice is given to the person.