

Datum: 2006-12-06

Nobel Biocare AB
P O Box 5190
SE- 402 26 Göteborg

This text is published for information purposes only. It is a translation of a decision and has as such no official, legal status. Please notice that the pages 5,6,7,8 ½ of 9 from the original decision are not translated.

Market surveillance of dental implants NobelDirect and NobelPerfect

Decision

The Medical Products Agency directs Nobel Biocare AB to

- clearly indicate possible causes of raised marginal bone resorption as well as describe how this can be avoided in the instructions for use and training programs connected to the NobelDirect and NobelPerfect dental implants
- in the instructions for use and marketing materials indicate the user qualifications and skills required to use the implants safely
- inform customers and authorities for medical devices in the countries concerned in an Advisory Notice of the measures listed above and the background
- submit the revised instructions for use when completed to customers and the named authorities
- no later than 8 January 2007 submit a plan including the time plan for the above measures to the Medical Products Agency
- refrain from promotional activities for the NobelDirect and NobelPerfect implants until the plan has been carried out.

If Nobel Biocare AB does not submit the requested plan including time plan within the indicated answering time, the Medical Products Agency may take the decision for a market ban on the products.

Legal basis

5, 6, 9, 12 and 13 §§ the (1993:584) Swedish Medical Devices Act, 3 and 12 §§ and annexe 1, 2 and 10, the Medical Products Agency regulations for medical devices (LVFS 2003:11)

Description of the issue

On Sunday, 16 October 2005, Professor Tomas Albrektsson, Chair of the Department on Biomaterials at the Sahlgrenska Academy, Göteborg University, appeared on a Swedish television news program with information about unusually high bone resorption of the dental implant NobelDirect, manufactured by Nobel Biocare AB (the company).

The oral surgeon Mats Hellman, who together with Albrektsson is included in the grouping hereafter called the Göteborg group, submitted a brief notification on 17 October 2005 to the Medical Products Agency with information that the new implant, NobelDirect, exhibits rapid marginal bone loss, which normally is not seen around a standard implant. Bone loss in many cases very likely can give rise to problems with the mucosa and loss of the implant.

On the same day, Nobel Biocare AB contacted the Medical Products Agency and reported that on 23 May 2005, Professor Lars Sennerby of the Dept. of Biomaterials, Göteborg University and member of the Göteborg group, had contacted the company about an observation of higher than expected bone resorption. The company reported that at that time, they had requested to receive Sennerby's material but as of October 2005 still had not seen it.

Hellman submitted the following supplementary documents after the request from the MPA.

During the period 29 October 2003 to 23 August 2004, Hellman treated 42 patients with NobelDirect implants from Nobel Biocare AB. 21 patients have taken part in a scientific study with Nobel Biocare AB. The study was approved by the Research Ethics Committee in Uppsala.

Hellman had seen abnormal tissue response against the NobelDirect implant compared with earlier implant treatments with the Brånemark implant. Four implants in three patients were removed. X-ray analyses showed that more than 30% of the implants showed more than a 2-mm marginal bone loss during the first year, which is 3 to 4-fold more than the treatment team's experience with the Brånemark implant in similar treatments. About 20 implants showed periimplantitis-like, crater-formed defects, which is something seldom seen with the Brånemark implants during the first year of implant load. This leads to bad esthetics when the gray, raw oxidized surface comes into contact with the soft tissues with a gray coloured ring around the crown. The abnormal tissue reactions described earlier have been communicated to Nobel Biocare AB on repeated occasions.

Based on this meagre information, the MPA initiated an investigation to illuminate the situation. The MPA requested confidentially to receive more hard data from Hellman and Sennerby.

In addition to the NobelDirect implant, the MPA's market surveillance includes the very similar implant, NobelPerfect. Both are medical devices in risk class IIb.

In November 2005, the MPA reviewed the documentation that was the basis for the CE marking and found nothing that diverged from the requirements in the rules. Nobel Biocare's clinical evaluations were built upon the premise that the materials, surfaces and large parts of the geometrical design of the new implants have been used earlier in existing and more tried-and-tested products. No new difficulties in handling were foreseen in the original risk analysis.

At a meeting with the MPA on 20 December 2005, Nobel Biocare AB reported their views on bone level follow-up as well as actual information on their on-going prospective studies T-106 A+B and T-108 where an earlier study T-091 with the company's Brånemark System is used as comparative material. Data collected during 12 months showed that for 14% of 122 implants, the marginal bone level reduction was measured at 3 mm or more.

In a letter dated 9 January 2006, the company reported an excerpt from the customer complaint register concerning the implant type NobelDirect. It indicated 743 losses of implants out of 55 017 sold implants, which is equivalent to 1.35%, and was said to be at the same level as the company's other implants.

During a meeting at the MPA on 25 January 2006, members of the Goteborg group (Lars Sennerby, Mats Hellman and Pär-Olof Östman) presented preliminary information on marginal bone level reduction with 3 mm or more in ca. 30% of the implants studied. They plan to publish the final information in scientific journals later on. No form of systematic documentation or X-rays was submitted at the meeting.

On 6 February 2006, the MPA arranged a meeting between representatives for Nobel Biocare AB and the researchers and clinicians led by Tomas Albrektsson, who had criticized the NobelDirect implant. One purpose of the meeting was to re-establish a constructive dialogue between the researchers and company. Also at the meeting was Professor Björn Klinge who was called in as the MPA's external scientific expert on the question. Again, none of the requested documentation in the form of scientific articles or X-rays was submitted.

In a letter to the MPA that arrived 23 February 2006, Albrektsson and Sennerby requested, "...that the MPA immediately stops NobelDirect when used with a punch procedure for placement, immediate preparation and direct loading." They claim in their letter that "NobelDirect is an inappropriate implant *if it is used in the manner Nobel Biocare recommends.*" The professors indicate that in direct discussions with the clinicians who reported good treatment results in Nobel Biocare's studies, it came to light that these clinicians did not follow Nobel Biocare's indicated recommendations for using the implant. Among other things, Albrektsson and Sennerby claim that these clinicians in all cases have used a flap procedure and/or avoided direct loading of the implant by not placing it directly in occlusion following the operation.

Om May 2006, the MPA appointed an expert group including Professor Björn Klinge, Professor Per-Olf Glantz and Associate Professor Per Åstrand to assist the MPA with an independent expert review. Nobel Biocare and the Göteborg group approved composition of the expert group.

The expert group statement was submitted to the MPA on 18 July 2006. It is ascertained in the findings that: “Especially the supplementary material that Nobel Biocare sent to the MPA after 15 June 2006 contains data that support the possibilities to reach good treatment results when using the implant NobelDirect. In the material, however, there are no explanations for the observed, unexpected large bone losses in a relatively large number of patients, for instance, in the company’s own study T-106.”

In addition, the MPA expert group came to the following conclusion: “The studied documents and X-rays show that during the short observation periods under review, the NobelDirect implant can function satisfactorily as prosthetic retention element. For some patients, however, the reported bone loss is more extensive than expected. The percentage of patients with unexpectedly large bone loss is also larger than expected, especially when considering the advantages that Nobel Biocare has indicated with NobelDirect.

The analysis of the available supporting documents in addition show that the majority of the company’s product documentation claimed advantages with NobelDirect lack support in our supporting documents. As a result, the documentation concerned must be revised so that these recommendations, advice and directions are correct. It is our opinion that NobelDirect should not be marketed before completing the revisions.

Finally, in consideration for patient safety and the principle *Primum non nocere*, our judgement is that even after revising the product documentation, the implant of type NobelDirect should be used with great care until Nobel Biocare can present acceptable scientific documentation with good treatment results throughout for NobelDirect.”

In addition to the material in the MPA file, the expert group also reviewed three scientific articles and a CD-ROM with X-rays received from Albrektsson and Sennerby. The three manuscripts and CD were received at the MPA on 11 August 2006 and copies were immediately forwarded to Nobel Biocare’s representative.

Before this, Nobel Biocare AB informed the MPA in a letter on 9 August 2006 that they would have a temporary stop in distribution of sales promotion materials for NobelDirect and NobelPerfect until the MPA issued a decision in the matter.

After analysing the expert group findings and the materials sent in by the Göteborg group, Nobel Biocare AB sent in comments about the expert group findings on August 2006. Nobel Biocare AB points out that the expert group prepared its findings before the company had access to the Göteborg group’s materials and therefore Nobel Biocare AB could not conduct their own analysis before the findings were prepared. Following analysis of the materials with the help of in-house and external expertise, Nobel Biocare AB is of the opinion that the supporting documentation shows great inadequacies and considers the value of the expert group’s report to be limited.

Nobel Biocare AB

- claims that the Göteborg group's materials are not transparent on a number of points
- is of the opinion that how the X-rays are interpreted is a key question and claims that the Göteborg professors' materials exaggerate bone level changes when compared with the company's own analysis.
- is of the opinion that that the only relevant comparison between a one-piece implant and two-piece implant is the bone level in relation to the reference point on the implant because of the phenomenon of bone remodelling during the early stage of healing. Nobel Biocare expresses their surprise that the expert group chose not to comment on this question of the method for comparing the two types of implants.

In their comments, Nobel Biocare AB also reports its summary of available results after 1 or 2 years or more. Nobel Biocare AB has submitted comments on the Göteborg group's manuscript and has also described the results of their own analysis and the related X-rays. In the comments, they submit tables and diagrams from the results of their own studies compared to the re-evaluations of the Göteborg group's materials by the expertise called in by Nobel Biocare.

At Nobel Biocare AB's request, the MPA arranged a meeting with the company on 10 October 2006, where the company was given the opportunity to clarify the information submitted earlier.

Nobel Biocare AB sent supplementary information to the MPA on 13 October 2006 and 31 October 2006, and included some two-year data showing that for 8% of 62 reported implants, the marginal bone level reduction was measured to 3 mm or more. The expert group reviews the report of the two-year data and submits comment on 21 November 2006 where they adhere to their earlier expressed criticism. Over and above that, additional written exchanges have taken place in the matter.

Existing legislation

Not translated - 5,6,7,8 ½ of 9

The Medical Products Agency judgement

The issue for the MPA to decide is if the information on the early appearance of loss of jawbone, called marginal bone resorption, surrounding Nobel Biocare's dental implants NobelDirect and NobelPerfect has such significance that the agency should decide on a limitation or ban to sell this type of implant or otherwise order the manufacturer to take measures the agency finds justified.

The danger with marginal bone resorption is that when it comes to a certain level, there is a risk that the implant loses a stable attachment in the jawbone and loosens or that resorption affects the soft tissue adaptation to the implant to such a degree that the implantation is considered a failure. It happens that this causes the implant to be dispelled.

That the implant permanently heals securely and in other respects gives the expected result are the final goals of the treatment. How well these are reached is usually reported as cumulative survival rate (CSR). CSR indicates the share of implants still in place after a certain time of all implanted. The relationship between marginal bone resorption and CSR can be expressed as the more implants in a treatment series that show extraordinary bone resorption, the greater the probability that the CSR will be affected negatively.

There is support for the view that the limit for acceptable marginal bone resorption can be set at 3 mm during the first year for implants with bone anchor and abutment mounted or manufactured as one unit. There is similar support for how large a proportion in a treatment series can be allowed to show marginal bone resorption >3 mm. From the compilation where frequency distribution is reported or can be calculated for this type of implant, the conclusion can be drawn that the share is expected to remain within single digit percentages with good margins. The manufacturer Nobel Biocare AB has not presented any acceptance criteria.

The level for acceptable CSR and at what rate it can be permitted to decrease over time has not been established. Actual compilations, however, give support for the level of what can be seen as positive treatment results are clearly more than 90% after the first year.

Concerning the reasons for marginal bone resorption, these can in principle be divided in factors related to the patient, the actual implant and to the handling, i.e. insertion and following preparation. It can be assumed that the combination of these factors transpires in a treatment series and even in one and the same case. Generally, it can be difficult to establish the exact reason; it is often given with some degree of probability. Accumulation of marginal bone resorption >3 mm in a treatment series can, however, indicate there is a common explanation.

The information on marginal bone resorption and CSR in the table below was taken from the documents that are included in the matter. Thus the results are taken from the report "Preliminary results from a retrospective study on the NobelDirect one-piece implant" by Lars Sennerby of the Göteborg group. The times for follow-up vary between 1 and 18 months with an average of 10.8 months. The X-rays that Sennerby's numbers for marginal bone resorption are based on were reviewed by independent radiology expertise commissioned by Nobel Biocare. From the X-rays of the original 220 implants, 170 were assessed to give measures and the results are reported in the table Revised Sennerby.

The table includes further numbers from Nobel Biocare's report "Prospective studies on NobelDirect and NobelPerfect one-piece implants" based on the one-year follow-up in the company's prospective three-year study T-106 A+B. Four clinicians participated in the study. One of these, Clinic 4, has an association with the Göteborg group and is reported separately in the report and the table. Finally for purposes of comparison, the report includes the first year's data from the T-091 study in which one of the company's other implants, Brånemark System, was used. These numbers are also reported in the table.

	Sennerby	Revised Sennerby	T-106 A+B	Clinic 4	T-091
Number of implants	220	170	122	67	95
Marginal bone resorption, mean (mm)	2.2	1.2	1.40	1.56	1.19
Standard deviation (mm)	1.4	2.2	1.44	1.43	0.85
Share >3mm	30.7 %	15.3 %	14 %	13 %	1 %
CSR	92.8 %	-	98.3 %	-	97 %

As shown, the percentage shares with marginal bone resorption >3 mm throughout are double-digits for NobelDirect and NobelPerfect, that compared with 1% for Brånemark System in T-091. CSR in T-106, fulfils the high demands, while the 92.8% in Sennerby's report should be seen to lie at the lower limit for the expected. Recently, Nobel Biocare supplemented T-106 A+OB with results from the 2-year follow-up. This includes 62 implants whereof none from Clinic 4. The share of implants with marginal bone resorption >3 mm now amounts to 8% and CSR to 98%, which must be considered to point to that bone resorption in this group at least did not progress during the second year. However, the MPA's position is that this 2-year data in spite of everything does not eliminate the view that NobelDirect and NobelPerfect in these treatment series are associated with early appearance of raised marginal bone resorption unexpectedly often.

In the matter of whether a likely reason for the unexpected incidence of marginal bone resorption >3mm can be identified, the MPA makes the following assessment. When it comes to factors related to the patient, there is reason to assume that those who were included in the treatment series above do not differ from the average and that they were found appropriate for the chosen treatment concept. The NobelDirect and NobelPerfect implants are manufactured with a bone anchor and abutment in one unit and represent inasmuch a new construction, but they correspond in the choice of materials, surface treatment and other construction details with documented, well-functioning implants from Nobel Biocare, such as the Brånemark System.

When it comes to handling, both Nobel Biocare AB and the Göteborg group have presented the explanation that the deviating results could very well be due to details in the procedure with implantation and the following preparation. The MPA does not find anything that convincingly opposes this.

This leads the focus to the instructions for use. Nobel Biocare's position is that the deviating results are because the instructions are not followed and the company assumes that these contain the guidance that is required. The MPA has the following comments. NobelDirect and NobelPerfect are intended to be used in a treatment concept where it may be questioned whether it was sufficiently tested before placed on

the market. When experiences from clinical applications are now beginning to be available, it is the company's responsibility to take these into consideration and take measures to see these are used. Nobel Biocare AB states that some changes in the manuals have been made but information is still lacking such as the company's information that bone resorption can be expected to the uppermost thread on the implant's bone anchoring part. This does not necessarily mean that just this has had significance for the results, but it is a reminder that the usefulness of the instructions for use is not only determined by the instructions they contain but also by the instructions they lack.

The MPA finds it appropriate for Nobel Biocare AB to broaden the risk analysis concerning handling the actual implant with the view to insert modifications in the instructions for use, training activities and other marketing materials that henceforth reduce the probability of raised bone resorption.

In the wait for the result that this process is implemented, it is also appropriate for Nobel Biocare AB to continue to observe the same restraint in promotional activities for NobelDirect and NobelPerfect that the company decided upon in August 2006.

Against background of the above judgements and with the indicated measures from Nobel Biocare AB as well as in regards to the company's continuing registration of customer complaints so far have shown that NobelDirect and NobelPerfect in this respect do not differ from the company's other implants, the MPA finds no reason at present to prohibit the continued release of those actual implants to the market.

Finally, Nobel Biocare AB shall continue to inform the MPA on the results from the on-going studies with the actual implants and especially regarding marginal bone resorption and the survival of the implant.

The MPA has in this judgement of the issue and in its final position been guided by the expert group's conclusions.

Lennart Philipson took the decision in this case. Sven Jakobson reported the case. Arne Kardell, Ulrika Hörberg and Bo Lindström participated in the final processing.

How to appeal:

- to the County Administrative Court in Uppsala County, see annexe 1.

On behalf of the Medical Products Agency,

Lennart Philipson

Sven Jakobson