IGJ position as a result of the ANSM decision relating to breast implants

Dear Minister Bruins,

On 4 April 2019 the French competent authority ANSM published a decision to, as a precautionary measure, withdraw 13 types of breast implants with a rough surface (macro-texture from 6 manufacturers from the market.,. ANSM has established an association between these breast implants and an increased risk of an extremely rare form of lymphoma called Breast Implant Associated-Anaplastic Large Cell Lymphoma or BIA-ALCL. As a result of the French decision, RIVM was asked to assess the scientific substantiation of this decision and provide an update of the most recent publications. The Health and Youth Care Inspectorate [Inspectie Gezondheidszorg en Jeugd] (IGJ) has used the RIVM analysis to assess whether a change in its position regarding BIA-ALCL is necessary and whether other action needs to be taken. With this letter, the Inspectorate will inform you of its position and the action to be taken and the considerations on which this is based.

IGJ position

The decision by the French authority has, of course, caused the IGJ to consider whether a similar action is appropriate in the Netherlands. Medical devices, and therefore implants as well, must comply with the essential safety and effectiveness requirements. If safety is jeopardised after a product has been introduced onto the market, the Inspectorate is authorised, on the basis of Article 12a of the Medical Devices Act [Wet op de medische hulpmiddelen] to prevent damage to public health, to order the suspension or termination of the trade, import, export or delivery of a medical device, as well as the withdrawal of a medical device from the market.

RIVM was asked to make a scientific analysis, as soon as possible, of the recent, relevant literature (2017-today) and of the information on which ANSM based its decision. Based on the analysis which RIVM produced on 2 May 2019, the Inspectorate does not believe there is sufficient scientific evidence at this point in time to order breast implants to be withdrawn from the market. This point of view is clarified in more detail later on in this letter.

The Inspectorate has also considered the current risks of the medical device, based on their nature and scope, and their usefulness. The Inspectorate also carefully weighed out the fact that the alternatives for macro-textured breast implants are also associated with other risks. For example, the encapsulation of smooth implants frequently leads to complications which require removal of the implant and there is a greater risk of implant displacement. In addition, there is not enough information on the origin of BIA-ALCL to exclude an association with other types of breast implants. At the same time we are aware that society has questions and are concerned about the safety of breast implants. For these reasons, we are taking a variety of steps which we explain in more detail below.

It is also important that patients and healthcare providers continue to report adverse reactions to RIVM and Lareb's Dutch Reporting Centre for Adverse Effects of Medical Implants [Meldpunt Bijwerkingen Implantaten] (MEBI). The centre of expertise of this reporting centre analyses and interprets reports about possible adverse effects together with experts from the field of healthcare. If necessary, the centre of expertise can start an investigation into a certain implant with regard to which a large number of specific adverse reactions have been reported. They share these results in anonymised form with IGJ so appropriate action can be taken, if necessary.

Action by IGJ

The following is a more detailed description of the possibilities open to the Inspectorate and the actions taken.

<u>Allergan Biocell implants</u>

The Biocell implants from Allergan are currently not available on the market in Europe. Therefore, it is not relevant for the Inspectorate to take action in connection with these implants. If Allergan reapplies for a CE certificate, the notified body will assess whether the implants fulfil the essential requirements based on the latest scientific state-of-the-art. In cooperation with other European colleagues, we will monitor this process and take action as necessary.

Other macro-textured breast implants

A medical device that has successfully gone through all the necessary procedures via a notified body is authorised to access the (European) internal market. Withdrawing it from the market is a severe measure which IGJ can only take if there are sufficient grounds. The RIVM analysis has not revealed an increased risk of BIA-ALCL in the case of the other macro-textured breast implants. For that reason (among others) there are currently insufficient grounds for the IGJ to have these implants withdrawn from the market.

Notified bodies

Silicone breast implants are subject to the most strict authorisation system in terms of (European) legislation relatedto medical devices. A notified body assesses whether the medical device meets the applicable essential requirements, which are included in Annex I of the European Directive 93/42/EEC. An additional element of the authorisation regime is that the notified body investigates whether the manufacturing process and the medical devices meet the applicable requirements. Because breast implants are high risk medical devices, the notified body also has to assess the technical documentation. If the result of the entire conformity assessment is satisfactory, the manufacturer is allowed to place a CE mark on the product. The device may then be marketed throughout Europe. It has been established that CE marks have been issued for all silicone breast implants which are currently available on the market. After obtaining the CE certificate the manufacturers have the responsibility to continuously improve their products and modify the technical documentation in line with the information which becomes available after the market introduction. Manufacturers must collect that information viatheir Post-Marketing Surveillance (PMS) among other sources. Manufacturers must therefore include newly available information about BIA-ALCL in their PMS and modify their documentation such as the risk analysis and instructions for use accordingly and, as necessary, their products. The Inspectorate therefore believes there is sufficient groundto ask the notified bodies, in collaboration with other European competent authorities, to assess in the near future whether manufacturers have sufficiently incorporated the most recent data in their risk analysis and taken suitable measures. The Inspectorate is asking the notified bodies in question to carry out a dossier assessment and/or bring forward already planned assessments. The Inspectorate is doing this in consultation with the European competent authorities.

Information

The use of a medical device will always imply a certain risk which applies both to the risks of the product itself as well as the risks of the medical procedure. In addition, the knowledge and expertise of health care professionals play a role, as do patient-related factors. It is therefore important that health care professionals together with their patient/client list the advantages and disadvantages of breast implants and decide on the best treatment option for them based on this risk-benefit assessment.. The association of plastic surgeons (NVPC) has already done a great deal to improve information, for example by creating a patient leaflet for the surgical intervention with breast implants. Another important principle of healthcare law is that the patient gives consent for medical treatment to be carried out. After all, without informed consent the treatment would be an unauthorised violation of a patient's integrity. In order to give legally valid consent, a patient needs good information. That is why, before asking for this informed consent, a health care professional must first give a patient information about the intended examination or proposed treatment. This is more likely to be the case in the event of a less drastic or essential procedure than in the event of radical, risky or elective treatment. In the latter case the patient must, in any event, explicitly consent to the treatment and the health care professional will also record this in the patient file. The presence of 'informed consent' continues to be one of the themes which the Inspectorate is monitoring in this context.

Dutch Breast Implant Registry

The Dutch Breast Implant Registry (DBIR) was created in 2015. It is used by plastic surgeons to register the breast implants they implant during surgery. They can also register implant removals and the reasons for doing so. Cases of diagnosed BIA-ALCL are also registered in the DBIR. Eventually this will generate valuable information about the incidence of BIA-ALCL and about the involved implant types. The Dutch Association for Plastic Surgery [Nederlandse Vereniging voor Plastische Chirurgie] (NVPC) and the umbrella organisation called the Association of Autonomous Clinics in the Netherlands [Zelfstandige Klinieken Nederland] (ZKN) have made registration obligatory for their members. Participation in the registry is also included in the healthcare indicators which care institutions report on

to the Inspectorate. The Inspectorate will encourage and make sure that healthcare providers actually register breast implants in DBIR.

Other action
Worldwide a great deal of attention is being paid to BIA-ALCL and its consequences. The Inspectorate will monitor developments closely through contacts with researchers, experts, other competent authorities in Europe and elsewhere and through participation in meetings like the one organised by RIVM last November. Upon any new information from these developments, we will continuously balance the pros and cons and decide whether additional action is necessary.

Facts Outcomes interpretation of RIVM research:

- RIVM has ascertained that the majority of cases of BIA-ALCL are known to involve Biocell implants from manufacturer Allergan, and that for Biocell implants are likely to have an increased risk of BIA-ALCL.
- Insufficient data are available to substantiate whether other types of implants present a similar risk as Biocell implants due to the small number of BIA-ALCL cases, the limited use of these implants and the use of different definitions for textures. There is also insufficient data available to substantiate scientifically that polyurethane coated implants (which do have a rough surface, but undergo an entirely different production process compared to the macro-textured implants) present a similar risk as Biocell implants. The majority of BIA-ALCL cases are found with Biocell breast implants. Cases of BIA-ALCL have also been found with other rough surface breast implants, also in the Netherlands. In the Netherlands, polyurethane coated implants are not used very widely and there are no cases of BIA-ALCL which are linked to this type of implants.

Considerations of IGJ in relation to BIA-ALCL:

- There is scientific evidence that women with breast implants are more likely to develop ALCL than women without breast implants.
- Scientific research has shown that BIA-ALCL is a very rare disease, also for women with breast implants. The chance is roughly 1 in 35,000 that a woman with a breast implant will develop this disease before reaching the age of 50 and a chance of 1 in 7,000 by the time they reach the age of 75.
- Scientific research has shown that, on average, it takes 10 years for BIA-ALCL to develop.
- If BIA-ALCL is caught early, treatment is usually curative. . The symptoms which may indicate BIA-ALCL — swelling of the breast, lump next to the implant — are clearly noticeable. The risk of dying from BIA-ALCL is very unlikely. That does not mean that the diagnosis can lead to a great deal of pain and distress among the patients involved.
- It is estimated that 200,000 women in the Netherlands currently have a breast implant. However, we do not know how many women have had breast implants in the past. Up to now there have been 52 known cases of BIA-ALCL since 1997, of which 20 cases were diagnosed in 2017 and 2018. This increase can be explained by, among other things, greater awareness and more attention for the disease and an increase in the number of women with breast implants in recent years.

Considerations of IGJ in relation to the implants:

- The majority of cases of BIA-ALCL are known to involve the Biocell implants from the manufacturer Allergan.
- The Biocell implants have not been available on the European/Dutch market since December 2018. The CE certificates have expired because certain information is missing from the technical dossier. The notified body has not (yet) issued any new certificates. In the same month Allergan recalled all implants which were still in stock.
- Insufficient data are available to substantiate whether other types of implants present a similar risk as Biocell implants due to the small number of BIA-ALCL cases, the limited use of these implants and the use of different definitions for texturing. There is no international, clear classification of implant types based on texture. Therefore, data which should provide an insight into preventing BIA-ALCL in relation to the type of texturing cannot be easily compared at international level.
- The risks of other than macro-textured implant types currently on the market are unknown. BIA-ALCL also occurs in combination with other types of breast implants. Additional risks needs to be taken into account with other implant types, for example, smooth implants require a different

operating technique. Additionally, smooth implants have a greater risk of displacement of the implant and capsular contracture, meaning that a re-operation may be necessary. The consequences of no longer using macro-textured breast implants are only visible in the longer term.

- In the event of a possible ban on certain implants, the number of available alternatives for health care professionals and patients/clients to choose from is limited. Doctors can provide fewer tailor-made treatments for their patients. A (large) group of women benefit from breast implants. Alternatively, they may be deprived of possible treatments.
- Not one implant is risk-free and there is always a possibility of complications or damage due to the implant, or due to the procedure to insert them. When using medical devices, a certain risk will always have to be accepted, whereby the doctor and patient/client will have to assess the risks and benefits. The medical devices legislation therefore assumes a continuous and informed monitoring of the balance between the risks and benefits. The legal point of view is not 100% safety, but to minimise the risks.
- There is no other European Member State that has adopted the measure of the French competent authority, ANSM.. Most other authorities are focusing, as we are, on informing patients, creating awareness among healthcare providers and on performing additional research into BIA-ALCL.

Yours sincerely,

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Inspector-General