Assessment of an epiretinal prosthesis and its implantation procedure

Summary of the health technology assessment report
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Project Management team

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The meetings and secretarial work were organised by Hélène DE TURCKHEIM.

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Composition of the working group

- Professor Jean-Louis ARNE, Ophthalmologist, TOULOUSE (31)
- Professor John CONRATH, Ophthalmologist, MARSEILLES (13)
- Mr. Bruno DELHOSTE, Optician, BAYONNE (64)
- Professor Jean-François KOROBELNIK, Ophthalmologist, BORDEAUX (33)
- Mrs. Christine MARION, Orthoptist, STRASBOURG (67)
- Professor Dominique MONNET, Ophthalmologist, member of the CNEDiMTS¹, PARIS (75)
- Mrs. Laurence PES, Orthoptist, MARSEILLES (13)
- Professor Jacques RIPART, Anaesthetist and Resuscitation Specialist, NIMES (30)

The opinion of the working group presented in this report has been validated by each of its members. Members of the working group were appointed on the basis of suggestions from the relevant associations or learned societies (French College of Anaesthetists and Resuscitation Specialists, Academy of Ophthalmology, French Orthoptics Association, National Federation of Opticians of France, Francophone Orthoptics Study and Research Society, Association of Professional Workers and Rehabilitation Therapists providing Assistance in Daily Life for people with visual impairment) who were contacted with a request for suitable candidates. Some healthcare professionals were also approached directly. In accordance with decree no. 2004-1139 of 26 October 2004 (Articles R. 161-84 to R. 161-86 of the Social Security Code), all members of the group completed a public declaration of interests, the purpose of which is to inform HAS of any conflict of interests some members of the group might have with a manufacturer. The public declarations of interest submitted by potential members of the working group were analysed in the light of the “Guide to declarations of interest and conflict management” published in March 2010. The analysis of the working group members’ declarations showed that there were no interests that could give rise to a major conflict. The composition of the working group and the declarations of interest were published on the HAS website (http://www.has-sante.fr) before the group’s first meeting. A reminder of these interests was also given at the start of the group’s meeting and when the working group’s opinion was presented to CNEDiMTS¹.

¹ National Committee for the Evaluation of Medical Devices and Health Technologies
Summary

Introduction and background

The National Committee for the Evaluation of Medical Devices and Health Technologies [CNEDiMTS] received a file requesting inclusion of an epiretinal prosthesis system called ARGUS II on the list of products and services qualifying for reimbursement [LPPR]. Since the associated procedures are not included in the Common Classification of Medical Procedures [CCAM], an evaluation of these procedures was also carried out.

This work was carried out according to a special approach linked with the innovative nature of this device, taking into account the high potential for improving the management of patients affected with retinitis pigmentosa. For innovative technologies, the aim of the Haute Autorité de Santé (HAS) is to reduce assessment duration as much as possible, while avoiding:

- a premature access to an insufficiently assessed technique, with an excessive health and/or financial risk as a consequence;
- a delay in making them available for the care system, when they bring about progress.

Scope of the assessment

The evaluation involves the ARGUS II epiretinal implant of Second Sight Medical and associated procedures (implantation, explantation, repositioning).

Method

The general method adopted by HAS is based on a critical analysis of the data from the scientific literature, the data submitted by the manufacturers and the position of healthcare professionals meeting in a working group. Furthermore, regarding this subject, HAS has interviewed the only expert in France to have implanted the ARGUS device, and also a patient association.

Critical analysis of the data

The data submitted by the manufacturer were analysed and complemented by a scientific literature search. This search did not find any clinical data providing a better level of evidence than the data supplied by the manufacturer.

A prospective, multi-centre, non-comparative feasibility study with 30 patients was analysed. The aim of this study was to assess the safety and efficacy of the ARGUS II system over a 3-year period.

Twenty-nine of the 30 patients had a retinitis pigmentosa as main diagnosis. On inclusion, all the patients had a visual acuity of > 2.9 LogMAR (i.e. residual light perception). The first 15 patients received an implant of the first-generation ARGUS II device and the next 15 the second-generation device (the subject of the application). None of the patients recruited was lost to follow-up.

The procedure was considered a success for all of the patients. Up to 3 years of follow-up, the results showed that chronic electrical stimulation did not worsen visual acuity of the implanted eye compared with the non-implanted eye. In patients who underwent laboratory tests, an improvement in visual function, orientation and mobility was shown when the ARGUS II system was switched on, with no effect on the patient’s residual vision. The four patients who derived most benefit from using the ARGUS II prosthesis were able to recognise words of four letters. However, for all of the tests carried out in the laboratory, a significant amount of data was missing (up to n = 16/30 depending on the tests) and there were different methods for carrying out the tests over time.

Concerning the capacity to perform vision-related activities of daily living (FLORA questionnaire combining self-assessment and assessment by a low-vision rehabilitation expert), 9 patients note a positive effect of using the ARGUS II prosthesis, 7 note a mild positive effect, 4 note a prior positive effect and 6 note no effect (4 missing data). Quality of life was evaluated through two questionnaires. At 12 months, neither the VisQOL questionnaire nor the Massof questionnaire revealed any clinically relevant effect of using the ARGUS II prosthesis.
system on the patients' quality of life. Beyond 12 months, the results cannot be interpreted because of the significant amount of missing data (over 10%).

In terms of safety, 20/30 patients had no serious adverse event linked with the procedure or the device. Twenty-one serious complications were recorded in 10 patients, 10 of which were in 2 patients: 3 cases of conjunctival dehiscence, 3 cases of conjunctival erosion, 3 cases of endophthalmitis (2 of which on the same day at the same theatre), 3 cases of hypotony, 2 reattachments of the retinal tack, 1 infectious corneal ulcer, 1 case of corneal opacity, 1 infectious keratitis, 1 rhegmatogenous retinal detachment, 1 tractional retinal detachment, 1 retinal tear and 1 case of uveitis. A total of 106 non-serious adverse events linked with the device or procedure were recorded in 25 patients (mainly conjunctival congestion, hypotension, choroidal detachments, irritation around the suture and ocular pain).

This is a feasibility study with a low level of evidence, whose protocol has undergone several amendments (modification of inclusion criteria, addition of endpoints). Only the tests described in the protocol have been reported. This study involves not only the device that is the subject of the application but also its previous version. The number of patients is small (n = 30) but it has to be considered in the light of the rare nature of the pathology concerned. It is also noted that the tests evaluating visual function were carried out under extreme conditions of contrast, which are rare in real life. Furthermore, depending on the time, the same test can be carried out using different methods (test of the capacity to follow a line on the ground and recognition of a door). Concerning the FLORA questionnaire, it is not guaranteed that the collection of measurements will be independent (possibility of intervention of one of the company’s technicians). Lastly, this study does not enable an assessment of the long-term effects (beyond 3 years) of chronic electrical stimulation on the retina and optic nerve.

**Working group opinion**

The experts in the working group expressed their opinions in the light of their knowledge of published data and their clinical practice. The proposals received a consensus and were validated by each of the group’s members.

**Clinical data**

The working group agreed that the study on the ARGUS II system was an exploratory phase with limited data available and small experience of the centres. The results on efficacy were encouraging but still not conclusive at this stage of the clinical assessment.

**Indications**

For the group, the indications of the ARGUS II system should be limited to: “patients affected by retinitis pigmentosa whose visual acuity is limited to the detection of hand movements (but not including the fingers) and who have had useful form vision in the past. If there is no residual light perception, the retina must be able to respond to electrical stimulation.”

In terms of contraindications, ARGUS II should not be implanted in patients who have blindness caused by a pathology other than retinitis pigmentosa.

**Pre-operative examination**

The working group emphasised the importance of the anatomical, functional, psychological and individual motivation pre-operative assessment.

**Composition of teams and training requirements**

The following should be present in the theatre:

- a two-person implantation team consisting of two ophthalmologists or one ophthalmologist and an operating assistant;
- certified anaesthesia personnel, i.e. an anaesthetist and resuscitation specialist and/or a state-certified anaesthetist nurse;
- a theatre nurse;
- a technician from the company that is marketing the device for the perioperative tests and for post-operative adjustments of the implant. These adjustments may be carried out by specially trained staff.
The ophthalmologists and operating assistants must have had theoretical and practical training specific to the implanted device. Practical training must be carried out by clinical proctoring at the implantation centre for at least the first three operations.

Technical environment

The only prerequisites are the availability of an operating theatre dedicated to vitreoretinal surgery and a post-operative monitoring room. Bearing in mind the small target population (20 to 30 patients per year in France), no more than three centres in France could aspire to the implantation of a retinal implant to guarantee optimum geographic distribution. Each two-person implantation team should perform at least three implantations per year.

Patient follow-up

Patients implanted with the ARGUS II system must be followed up regularly. An ophthalmological assessment and equipment checks must be carried out on D1, at W1, W2, W4 and at M3 and M6, and then every 6 months.

Patient rehabilitation

After any implantation, repositioning or explantation procedure, the working group agreed on the need to be able to provide patients with a rehabilitation protocol which would involve a multidisciplinary team trained in using the ARGUS II system. This team should consist of:

- an instructor in locomotion operating in the patient’s home and environment;
- an occupational therapist used to managing visual impairment in adults, operating in the patient’s home and environment;
- an orthoptist specialised in low vision;
- a psychologist;
- a psychometrician, if necessary.

The decision to stop the post-operative rehabilitation protocol must be made following a collective decision by the rehabilitation team.

Missing data

According to the working group, clinical investigation on the ARGUS II device must be continued in order to gather additional efficacy and safety data. A relevant study would be carried out in the patient’s usual environment and not in the laboratory and would involve an assessment of the capability to perform vision-related activities of daily living with a follow-up of at least three years.

Conclusion

In the state of the knowledge, the expected benefit of the ARGUS II epiretinal prosthesis is insufficient. To consider immediate generalised reimbursement of the device and procedure is premature in the light of the clinical data available.

However, the potential benefit of this technique is considerable. It is therefore essential to encourage and support the collection of additional real-life clinical data through well-conducted studies, considering the high potential of this innovative technology. This would make it possible to compensate for the disability of patients affected by blindness caused by a rare pathology, for whom to date there is no treatment. The proposal for a study as formulated by the working group commissioned by HAS would constitute a first step.

Consequently, in view of:

- the innovative nature of the device;
- the rare nature of the pathology concerned;
- the lack of a therapeutic alternative;
- the high potential for improving patients’ quality of life;
- the high potential for compensating for the disability linked with blindness;
- the probable favourable benefit-risk balance;
HAS recommends to support activity and device costing of the ARGUS II epiretinal prosthesis for a temporary period subject to collect further clinical data in accordance to the following recommendations:

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Multi-centre observational study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure</td>
<td>Implantation of ARGUS II epiretinal prosthesis</td>
</tr>
<tr>
<td>Control</td>
<td>Patient himself (system on versus system off)</td>
</tr>
</tbody>
</table>

**Primary endpoint**

Evaluation of the capability of patients to perform vision-related activities of daily living at baseline (pre-implantation) and at each follow-up period. The test would be based on the FLORA questionnaire including achievement of daily life tasks with social interaction tests, orientation and mobility tasks in a known or unknown environment, in or outside, with the system on or off and with or without aides. Attribution of a score for each task (impossible, possible / difficult, possible / moderate, possible / easy) as well as the identification how patients performed it (vision only, some vision, not vision). Lighting conditions and contrast have to be recorded.

Primary endpoint should be assessed by an independent low vision rehabilitation expert.

**Secondary endpoints**

- Evaluation of safety including explantation rate
- Evaluation of the number of hours of use per day
- Evaluation of the impact of chronic electrical stimulation on visual acuity
- Evaluation of contrast sensitivity by using gray-level scales
- Evaluation of the global patient satisfaction using validated scales
- Evaluation of the difficulty to use the device in daily life
- Demonstration of a possible correlation between the thickness of the ganglion cell layer and functional results