Policy Replaced with LCD L34555
Effective February 26, 2018

BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Retinal Prosthesis

Policy #:	627	Latest Review Date:	March 2017
Category:	DME	Policy Grade:	D

Background:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*

    - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
    - *Furnished in a setting appropriate to the patient's medical needs and condition;*
    - *Ordered and furnished by qualified personnel;*
    - *One that meets, but does not exceed, the patient's medical need; and*
    - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

Description of Procedure or Service:

A retinal prosthesis replaces lost photoreceptor function by transmitting external images to an array of electrodes or via light sensors placed in the epiretinal or subretinal space. The artificial retina could restore sight to patients with blindness secondary to retinal diseases, such as retinitis pigmentosa, hereditary retinal degeneration, and some forms of age-related macular degeneration. Several models of retinal prostheses are in development in the United States, Europe, and Asia. Only the Argus II system has been cleared by the U.S. Food and Drug Administration.

There is ongoing research interest in developing an artificial retina that could restore sight to patients with blindness secondary to retinal diseases, such as retinitis pigmentosa, hereditary retinal degeneration, and some forms of age-related macular degeneration. Two approaches are being developed. The first is implantation of electrode arrays in the epiretinal or subretinal space to stimulate retinal ganglion cells. A second approach is the implantation in the subretinal space of light-sensitive multiphotodiode arrays, which stimulate the remaining photoreceptors in the inner retina. Use of a multiphotodiode array does not require external image processing. The latter approach is being evaluated for degenerative retinal diseases such as retinitis pigmentosa, in which outer retinal cells deteriorate, but inner retinal cells remain intact for years.

Research in the United States has begun with a first-generation, 16-electrode device (e.g., the ArgusTM 16; Second Sight Medical Products, Sylmar, CA), which permitted the distinction between the presence and absence of light. The Argus II Retinal Prosthesis System (Argus II) is the second-generation device, which has 60 electrodes. The retinal prosthesis, with the electrode array, is surgically implanted in and on the eye. The system's external components includes of a small external video camera, held on eyeglass frames, that captures images then processed by an externally worn microcomputer. These signals are transmitted to an antenna in the prosthesis, an electronics package in the superior temporal quadrant and an electrode array implanted in the back of the eye, which in turn stimulates the optic nerve. It is hoped that further generation devices, containing more than 1000 electrodes, will provide more detailed vision. Three government organizations provided support for the development of the Argus II: Department of Energy, National Eye Institute at the National Institutes of Health, and National Science Foundation. They collaborated to provide grant funding, support for material design, and other basic research for the project.

Other devices in development, none of which are approved or cleared by the U.S. Food and Drug Administration, include the following.

- The Alpha IMS was developed at the University of Tubingen, with the electronic chip design provided by the Institute for Microelectronics (IMS), Stuttgart. The second-generation Alpha IMS device has wireless power and signal transmission and is produced by Retina Implant AG (Germany). The microchip is implanted sub-retinally and receives input from a multiphotodiode array with 1500 elements that moves with the eye, senses incident light, and applies a constant-voltage signal at the respective 1500 electrodes. The multiphotodiode array transforms visual scenes into corresponding spatial patterns (38-40 pixels) of light intensity-dependent electric stimulation pulses with a maximum visual field of 15°.

- The Boston Retinal Implant Project (BRIP) uses an external camera mounted on a pair of glasses and a 100-electrode array. The image obtained by the external camera is translated into an electromagnetic signal transmitted from the external primary data coil mounted on a pair of glasses to the implanted secondary data coil attached to the cornea. Most of the volume of the implant lies outside the eye, with transscleral cables connected to a subretinal electrode array. The BRIP is a joint effort of MIT, the Massachusetts Eye and Ear Infirmary, the VA Boston Healthcare System, and the NanoScale Science & Technology Facility at Cornell University.
- EPIRET3 retinal implant (Philipps-University Marburg, Germany) was a wireless system that consists of a semiconductor camera on the frame of a pair of glasses and a transmitter coil outside the eye, which sends electromagnetic signals to a receiver coil in the anterior vitreous (similar to an intraocular lens), which passes them on to a receiver microchip. A stimulator chip then generates the stimulation pulses and activates a selection of 25 electrodes placed on the epiretinal surface via a connecting micro cable.
- Intelligent Retinal Implant System (IRIS; Pixium Vision, Paris, France) uses an external camera integrated with a pair of glasses and linked by wire to a pocket computer. Receiver electronics connect via a scleral tunnel to an electrode array on the surface of the retina. Pixium Vision is also developing PRIMA, which uses a subretinal implant.
- Learning Retinal Implant (Intelligent Medical Implants, Zug, Switzerland) uses an external camera on the frame of a pair of glasses and wireless data and power transfer. Receiver electronics connect via a scleral tunnel to an epiretinal implant. A retinal encoder with 100 to 1000 tunable spatiotemporal filters simulates the filtering operations performed by the ganglion cell and allows individual calibration to improve each patient's visual perception.
- Microelectrode-STS (suprachoroidal-transretinal stimulation) system (Osaka University, Japan) places its 9- electrode retinal prosthesis in a scleral pocket with a reference electrode in the vitreous cavity. A video camera is used to detect a visual object. Because the electrodes are at a greater distance from the retina, the resolution of the image may be lower than other devices. A proposed advantage of the STS prosthesis over epi- or subretinal prostheses is the safety of the surgical procedure, because the electrodes do not touch the retina.

Policy:

For dates of service on or after February 26, 2018 refer to LCD L34555

Effective for dates of service prior to February 26, 2018:
Blue Advantage will treat **retinal prostheses** as a **non-covered benefit** and as **investigational.**

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most

appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The most recent literature review was performed through January 25, 2017.

Retinal Prosthesis

A 2016 technology assessment prepared for the Agency for Healthcare Research and Quality (AHRQ) included a systematic review of the literature on retinal prostheses. Reviewers included studies on the Argus II, the only retinal prosthesis cleared for marketing in the United States, as well as other retinal prostheses. Outcomes of interest were visual function, visual acuity, laboratory-based visual performance measures, day-to-day function, and quality of life. In their qualitative summary of the literature on retinal prostheses, reviewers concluded that the strength of evidence was insufficient for all outcomes.

One single-arm study with 30 patients has evaluated the Argus II retinal prosthesis: numerous articles have been published on its findings and on sub-studies conducted on some or all of the participants. The study was prospective and multicenter, with sites in the United States and Europe. It included patients with retinitis pigmentosa (U.S.) or outer retinal degeneration (Europe) who had bare light perception or no light perception in both eyes.

In 2012, Humayun et al reported interim (minimum 6-month) results on 3 types of visual acuity tasks using a computer and 2 types of real-world utility tests. The computer tasks included square localization (locating a high-contrast white square of light on a black background), direction of motion (indicating the direction of a high-contrast bar moving across the screen), and grating discrimination (discriminating among square-wave gratings of different special frequencies presented on a monitor). Patients performed better on all 3 computer tasks with the system on than off. In terms of the 2 real-world utility tests, with the system on, subjects had a 54% success rate in finding a door compared with a 27% success rate with the device off and had 68% success rate in following a white line on a dark floor compared with 23% success rate with the device off. Although all subjects were able to perceive light when the system was stimulated, the Argus II did not affect full-field light perception.

In 2016, da Cruz et al reported on 3- and 5-year results of the visual acuity tests. Patients performed significantly better on the 3 computer tasks with the device on compared with off. For the simplest task, square localization, 89% (25/28) of patients tested did better with the device on and at year 5, 81% (17/ 21) of patients tested did better with the device on. For grating discrimination, the most difficult assessment, 33% (9/27) of patients tested at year 3 did better with the device on and 38% (8/21) of patients tested at year 5 did better with the device on.

In 2015, Ho et al reported on safety up to 3 years. At 3 years postimplantation, 23 serious adverse events were reported in 11 patients; the most commonly reported were conjunctival erosion (n=4), hypotony (n=4), conjunctival dehiscence (n=3), and presumed endophthalmitis (n=3). Five-year safety was reported by reported by da Cruz et al in 2016. As reported by da Cruz et al, only 1 additional SAE, a case of a rhegmatogenous retinal detachment, occurred after

the 3-year follow-up (4.5 years) after implantation. Three devices were explanted at 14 months, 3.5 years, and 4.3 years, respectively, after implantation. Two patients had experienced recurrent conjunctival erosion and the third experienced chronic hypotony and ptosis.

Several publications have reported on additional functional outcomes in patients participating in the Argus II study. Patients served as their own controls; performance was compared with the device in the on versus off position. In 2016, Geruschat et al reported observer-rated assessments of visual function using the multicomponent Functional Low-Vision Observer Rated Assessment (FLORA) instrument, which evaluates performance of 35 tasks. The tasks were grouped into 4 domains, visual orientation, mobility, daily life, and interaction with others). Twenty-six (87%) of the 30 enrolled patients were included in the analysis at a mean of 36 months (range, 18-44 months) after device implantation. All patients performed significantly better ($p<0.05$) in each of the 4 domains with the device on versus off, ranging from 19% to 38% improvement. Twenty-four (69%) of 35 tasks had a statistically significant improvement in outcome (ie, they were easier to perform) with the device turned on versus off.

A 2013 study reported on letter and word reading at 20 months in 21 of the patients participating in the Argus II study. Correct letter reading ranged from 51.7% to 72.3% with the device on, compared with 15.3% to 17.7% with the device off. The average time for correctly identified letters with the device on ranged from 47.7 seconds to 68.6 seconds. Subjects who successfully completed the letter identification task proceeded to the next task. Six subjects were able to consistently read letters of reduced size. The smallest letter identified was 0.9 cm for 1 subject, but preferred letter size was as much as 22.6 cm. Four subjects were able to correctly identify 2-, 3-, and 4-letter words.

In 2014, Kotecha et al reported on further testing of 6 patients from one of the Argus II study sites who had at least 3 years of follow-up; reaching and grasping outcomes were assessed. The test consisted of picking up a white cube from a table covered with black felt and illuminated from above, and was conducted with the electrode array on, array off, and scrambled (ie, array stimulated with a random, scattered input), in a random order. Also randomized was the location of the object, which could be placed in 1 of 4 positions. To eliminate the use of any residual vision among participants, certain patients had both eyes taped shut during the test. After 4 to 6 weeks, patients were retested to examine repeatability of performance. The percentage of successful grasps was significantly higher with the device on (69%) compared with device off (0%); this finding was maintained at the second visit. With the signal scrambled, success rates were 59% on the first visit and 28% on the second visit. There were no significant differences between “on” or “scrambled” conditions for movement onset, time to object contact, or path deviation ratio, which was defined as the “deviation of the movement trajectory from a straight route between the starting and object contact wrist positions.”

In 2016, Dagnelie et al evaluated performance on several functional tasks in 28 of 30 study participants who had been implanted with the device between 6 months and 3 years previously. The 3 tasks were intended to have real-world value. Performance was compared with the retinal prosthesis device on and off. Task 1 was sock sorting, sorting a mixed pile of socks into piles of pure white, pure black and grey socks. The sock task was performed 4 times; with the device on versus off and the surface of the table covered in a known color of cloth, and on versus off on a

bare table. Task 2 was sidewalk tracking. Subjects were asked to walk along three 6-meter stretches of sidewalk (straight, curved, or angled) within 1 meter of the edge without stepping off the pavement. No canes or other mobility aids were used. The task was scored by the number of times the subject moved out of bounds (ie moved off the pavement or more than 1 meter from the edge). Task 3 was walking direction discrimination. Subjects were seated and markers were placed 0.3 meters (10 feet) away in either direction. Initially a tester was placed at each marker. During the test, every 15 seconds there was an audible beep and a tester passed in front of the subject who guessed which direction they were walking.

On all 3 tasks, subjects performed significantly better with the device on versus off ($p<0.05$). (For the sock sorting task, results were presented in figures and precise numbers/percentages were not available). With a cloth-covered table, subjects sorted approximately 70% of the socks correctly with the device on and 30% correct with the device off. With a bare table, subjects sorted approximately 50% of socks correctly with the device and 30% with the device off. For the sidewalk task, subjects walked out of bounds a mean of 6.85 times with the device off and a mean of 4.93 times with the device on. For the walking direction discrimination task, 15 (56%) of 27 subjects performed significantly better than chance with the device on and 4 performed significantly better than chance with the device off. Although statistically significant, clinical significance of the differences in performance on the 3 tasks is more uncertain.

Summary of Evidence

For individuals who have blindness secondary to retinal diseases who receive a retinal prosthesis, the evidence includes a prospective single arm study evaluating the device approved by the Food and Drug Administration (FDA) and a systematic review of studies on various devices. Relevant outcomes are functional outcomes, quality of life, and treatment-related morbidity. A 2016 systematic review included studies on the FDA-approved retinal prosthesis device as well as devices unavailable in the U.S.; the overall conclusion was that the evidence on retinal prostheses is insufficient on all outcomes of interest. One study with 30 patients has evaluated the single FDA-approved device (the Argus II) and numerous articles on this study have been published. Primary outcomes included 3 computer-based visual acuity tests. At 3- and 5-year follow-up visits, patients performed significantly better on the 3 computer tasks with the device on compared with off. Performance on the most difficult task, grating discrimination, was still relatively low with the device on. Sub-studies have tested performance on more practical tasks. These studies tended to find significantly better performance with the device on but differences between groups may not be clinically meaningful. The same 30 patients have been evaluated multiple times and as a result of multiple testing, their performance may differ from other individuals with the device. Additional prospective studies and additional evaluations of the ability to perform practical tasks with clinically meaningful impact on health outcomes are needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

No guidelines or statements were identified.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Key Words:
Argus II, Retinal prosthesis, Boston Retinal Implant, Intelligent Retinal Implant System, EPIRET3 Retinal Implant, Alpha IMS Subretinal Implant

Approved by Governing Bodies:
In 2013, the Argus II retinal prosthesis (Second Sight Medical) was cleared for marketing by the U.S. Food and Drug Administration (FDA) through a humanitarian use device exemption (HDE). HDE approval is limited to those devices that treat or diagnose fewer than 4000 people in the United States each year. The Argus II system is intended for use in adults, age 25 years or older, with severe to profound retinitis pigmentosa who have bare light perception (can perceive light, but not the direction from which it is coming) or no light perception in both eyes, evidence of intact inner layer retina function, and a previous history of the ability to see forms. Patients must also be willing and able to receive the recommended post-implant clinical follow-up, device fitting, and visual rehabilitation. FDA product code: NBF.

Benefit Application:
Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

Current Coding:
CPT Codes:

0100T	Placement of subconjunctival retinal prosthesis receiver and pulse generator, and implantation of intra-ocular retinal electrode array, with vitrectomy
0472T	Device evaluation, interrogation, and initial programming of intra-ocular retinal electrode array (e.g. retinal prosthesis), in person, with iterative adjustment of the implantable device to test functionality, select optimal permanent programmed values with analysis, including visual training, with review and report by a qualified health care professional. **(Effective 07/01/2017)**
0473T	Device evaluation and interrogation of intra-ocular retinal electrode array (e.g. retinal prosthesis), in person, including reprogramming and visual training, when performed, with review and report by a qualified health care professional. **(Effective 07/01/2017)**

HCPCS:

C1841	Retinal prosthesis, includes all internal and external components

V2799 Vision item or service, miscellaneous

References:

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14. Zrenner E, Bartz-Schmidt KU, Benav H, et al. Subretinal electronic chips allow blind patients to read letters and combine them to words. Proc R Soc Biol Sci. May 22 2011; 278(1711):1489-1497.

Policy History:

Adopted for Blue Advantage, March 2016
Available for comment March 18 through May 1, 2016
Medical Policy Group, March 2017
Medical Policy Group, December 2017

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.