MED EL
CORPORATION

COMBI 40+ Package Insert

DEVICE DESCRIPTION

The COMBI 40+ Cochlear Implant System is a cochlear implant system consisting of the Implant C40+, all components of the CIS PRO+ Patient Kit, all components of the TEMPO+ Patient Kit, the DIB (Diagnostic Interface Box) System, the Detector Box, and the Surgical Kit. The implanted portion, the Implant C40+, is surgically implanted under the skin behind the ear. It consists of a ceramic housing, an active electrode array that is inserted into the cochlea during surgery, and a reference electrode, which is placed under the temporalis muscle. There are two patient kits for the COMBI 40+ Cochlear Implant System: the CIS PRO+ Patient Kit and the TEMPO+ Patient Kit. The function of the patient kits is basically the same. The major difference is that the TEMPO+ Speech Processor is a modular system, which can be worn entirely at ear level, and the CIS PRO+ Speech Processor is worn on the body.

For both devices, an external microphone picks up sound from the environment and sends it to the speech processor. The speech processor analyses the sound signal from the microphone according to the selected speech coding strategy, and transforms it into a coded electrical signal that is sent to the externally worn coil. This coded signal contains information about how to stimulate the individual electrodes so changes in pitch and loudness can be perceived. The coil, which is magnetically held in place over the implant, sends the coded signal across the skin to the implant package via an inductive link. The energy necessary for stimulation is also sent via the inductive link. The implant decodes the signal and sends a corresponding pattern of rapid stimulation pulses to the individual electrodes on the electrode array. These stimulation pulses travel along the auditory nerve to the brain, where the brain can categorize the sound and assign meaning. The COMBI 40+ Cochlear Implant System collects sound, processes the information, delivers instructions to the implant, and stimulates the electrodes with the appropriate pulse at a speed of up to 18,180 times per second. All electrode channels of the Implant C40+ are individually capacitively coupled to provide maximum protection against the accumulation of unintended Direct Current (DC)-charge.

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INDICATIONS FOR USE

The MED-EL COMBI 40+ Cochlear Implant System, hereinafter referred to as the COMBI 40+, is intended to provide the opportunity to detect and recognize auditory information through electrical stimulation of the auditory nerve for severe to profoundly hearing-impaired individuals who obtain little or no benefit from conventional acoustic amplification in the best-aided condition.

The COMBI 40+ is indicated for the following patient populations:

Adults of eighteen (18) years of age or older who have bilateral, sensorineural hearing impairment and obtain limited benefit from appropriately fitted binaural hearing aids. These individuals typically demonstrate bilateral severe to profound sensorineural hearing loss determined by a pure tone average of 70 dB or greater at 500 Hz, 1000 Hz, and 2000 Hz. Limited benefit from amplification is defined by test scores of 40% correct or less in best-aided listening condition on CD recorded tests of open-set sentence recognition Hearing In Noise Test sentences (HINT).

Children aged eighteen (18) months to seventeen (17) years eleven (11) months must demonstrate a profound, bilateral sensorineural hearing loss with thresholds of 90 dB or greater at 1000 Hz. In younger children, little or no benefit is defined by lack of progress in the development of simple auditory skills in conjunction with appropriate amplification and participation in intensive aural habilitation over a three (3) to six (6) month period. In older children, lack of aided benefit is defined as < 20% correct on the Multi-syllabic Lexical Neighborhood Test (MLNT) or Lexical Neighborhood Test (LNT), depending upon the child's cognitive ability and linguistic skills. A three (3) to six (6) month hearing aid trial is required for children without previous experience with hearing aids. Radiological evidence of cochlear ossification may justify a shorter trial with amplification.

INFORMATION FOR USE

Surgical Considerations:

Complete surgical instructions can be found in the Surgical Manual. All surgeons planning to implant the Implant C40+ must read the Surgical Manual prior to performing the surgery. Surgeons must also be experienced in mastoid surgery and the facial recess approach. The following are some key points covered in the Surgical Manual:

- The most fragile points of a cochlear implant are the connections of different parts. In the case of the Implant C40+, the electrodes connect to the implant housing tangentially on the side of the housing to provide maximum reliability and support from bone underneath. The Implant C40+ package is the same for the left and right ear. To allow for the electrode to be guided toward the mastoid,

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The User Manual supplied with the COMBI 40+ is included with the Patient Kit. It is important that users read and understand this manual completely. It contains useful information for the COMBI 40+ and describes the user controls.

Re-Programming - Adults

While you are getting acquainted with the new sensations of sound, your perception of loudness may change over time. Larger changes are more common during the first few weeks following initial programming. In addition, your hearing ability may change and a different processor setting or strategy may be of advantage. Therefore, your implant center may require occasional programming adjustments and examination of the implant site. These are usually most frequent during the first year following surgery. After this, sessions normally occur annually. On average, a programming session takes between one and three hours.

Re-programming – Pediatric Patients/Guardians

Like all other cochlear implant systems, the settings of the speech processor will need to be readjusted or fine-tuned. This is because the sensitivity of the hearing nerves changes over time as they begin to get accustomed to stimulation from the implant. Your implant center will require that your child return at regular intervals to have the program and surgical site checked. The regularity of these fitting sessions will be decided by your implant center. On average, a programming session takes between one and three hours. The sessions will be more frequent during the first year following surgery, and may be required annually thereafter. Most patients need occasional adjustment of the program for as long as they use the implant.

CONTRAINDICATIONS

The Implant C40+ must not be implanted in situations where there is acute or chronic middle ear pathology, lesions or agenesis of the 8th cranial nerve, pathologies of the central auditory pathway, or Michel deformity present.

The patient should not be implanted if the individual is known to be intolerant of the materials used in the implant, there is an absence of cochlear development, the tympanic membrane is perforated, deafness is attributed to central damage of the acoustic nerve or the central auditory pathway, or if external or middle ear infections are present.

WARNINGS

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WARNING: Implantees with the COMBI 40+ Cochlear Implant System should not be subjected to MRI, should not enter the MRI suite, or come into close proximity to the source of the magnetic field. MRI involves the use of very strong magnetic fields, the effect of which could possibly dislodge the implant or demagnetize the internal implant magnet.

the housing must be placed at a different rotational angle for left and right ears, as indicated in the Surgical Manual.

- A well must be drilled for placement of the implant housing. Placement of the implant without drilling a recess into the bone must never be attempted, as it will almost certainly lead to eventual failure of the device.

- A channel must be drilled along the surface of the cranium to guide the active and the reference electrodes away from the implant housing and toward the mastoid cavity. Failure to drill a channel will likely result in premature electrode breakage.

- Please make sure to place the implant housing at sufficient distance from the mastoid cavity to allow for space for the TEMPO+ Speech Processor. A template is provided for guidance.

- The Implant C40+ electrode array has a slightly oval cross-section and was designed for ease of insertion and for deep placement in the scala tympani; and a suitable claw and forceps are provided for this purpose. In most cases where the scala tympani is free of obliteration, an insertion depth of ~ 31 mm should be accomplished. There is a silicone marker ring ~ 31 mm from the tip of the electrode, which should be up against the cochleostomy after insertion.

- The implant housing must be sutured to the skull, and care should be taken to assure that the suture does not cross over the electrodes.

- The Implant C40+ has a separate reference electrode lead. It is strongly recommended to place the reference electrode *under* the temporalis muscle onto the surface of the skull. Placement in or on top of the muscle will lead to gradual breakage of the reference electrode, which results in device failure. Please note that, depending on the type of incision you use, the reference electrode may pass underneath the incision.

We recommend the use of non-resorbable surgical suture for fixation of the implant package, and the use of suture, a titanium clip, or the split-bridge method for fixation of the electrode in the facial recess. The electrode array should be fixed so that no post-operative movement can occur.

After placement of the Implant C40+ housing and insertion of the electrode array, the position of the electrode array should be verified through radiology. An X-ray of the implanted ear is strongly recommended to verify electrode position in the cochlea.

User Manual

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- Inaccurate placement of the active electrode array may prevent acoustic perception with the device, and may require additional surgery.

- Surgical risks include the following: infection, inflammation, necrosis, hematoma, leakage of Cerebro-Spinal Fluid (CSF), damage to the facial nerve, pain, scarring of the wound, risks relating to general anesthesia.

- Possible post-operative side effects include the following: loud or uncomfortable sounds, pain during stimulation, stimulation of the facial nerve requiring re-programming of the device, partial or total failure of the implant requiring device removal, increased tinnitus, increased vertigo, impairment of the sense of taste.

- Any residual hearing will probably be destroyed in the implanted ear.

- *Electroconvulsive Therapy* must not be used on patients who use cochlear implants. It could cause damage to neural tissues and/or destroy the implanted device.

- *Monopolar electrosurgical instruments, including cautery,* must not be used in the vicinity of the cochlear implant, as they can induce current levels in the implant electrodes that may cause damage to neural tissues and/or destroy the implanted device.

- *Diathermy* must not be used in an area close to the cochlear implant, as it may induce current levels in the implant electrodes that may cause damage to neural tissues and/or destroy the implanted device.

- *Ionizing Radiation Therapy* close to the cochlear implant may cause damage to the implant.

- Electrical stimulation of the inner ear may cause some long-term side effects that are not yet known. Significant clinical experience with cochlear implants exists only since the early 1980's, and the COMBI 40+ employs stimulation modes that may in some way be different from previous devices. In general, current and charge density levels and other stimulation parameters are contained to levels that were shown to be safe in chronic stimulation in animals or prior cochlear implant models in humans.

- Mechanical trauma to the implant, such as those that could result from a blow to the head in the vicinity of the implant package, could result in failure of the device.

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PRECAUTIONS

- The speech processor is programmed to conform to each patient's individual needs. Patients must never use another person's speech processor because it is not suitable for them and may result in uncomfortably loud or unpleasant sensations.

- Some types of digital mobile phones may interfere with signals from the speech processor, and the speech processor may not work properly in conjunction with such devices.

- *Electrostatic Discharge* (ESD) may occur through either external or internal parts of the cochlear implant. The risk of ESD is particularly high in dry environments. Cochlear implant users should touch a metallic object before parts of the speech processor and its associated components come into contact with other surfaces or persons. ESD can corrupt the program that is stored in the speech processor and lead to temporary stimulation with loud and uncomfortable stimuli. The original program in the speech processor will in most cases be restored when the processor is turned off and back on. ESD may also cause damage to the implant itself, although it is highly unlikely.

- *Metal Detection Systems* and *Theft Detection Devices* may induce an electrical field in the cochlear implant, which can result in an audible sensation for some implant users. The materials used in the implant may activate the alarms on such devices. Cochlear implant patients are thus advised to always carry their Patient Identification Card.

- The cochlear implant or speech processor could in theory disturb airplane and other navigation systems. For this reason, the device should be considered like a personal computer and should be turned off before take-off and landing, as usually announced by airline personnel for electronic equipment.

- Please reference the appropriate device User's Manual for additional device specific general precautions.

ADVERSE EVENTS AND COMPLICATIONS

All patients implanted in the United States with the Implant C40+ standard electrode array during the Investigational Device Exemption (IDE) trial were included in the safety analysis. A total of 188 patients have been followed for a total experience of 1266 months. Adverse events were classified as medical/surgical or device related. Complications were classified as major if they required surgical intervention and minor if they resolved spontaneously or with non-invasive medical treatment.

There were no internal device failures in children or adults during the study period.

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ADULTS:

Twenty (20) patients out of one hundred and six (106) experienced twenty-two (22) adverse events or complications during the study period. One (1) event was classified as major because the resolution required revision surgery. The remaining twenty-one (21) events were classified as minor. All adverse events or complications have been resolved.

Medical/Surgical Complications: Adults

One (1) patient reported uncomfortable stimulation and was re-implanted due to the frequency and severity of the symptoms (the implant was fully functional).

One (1) patient has experienced episodic vertigo accompanied by a sensation of fullness and tinnitus and has been diagnosed with vestibular neuritis. The patient recently reported that the symptoms are much better and the device is used up to twelve (12) hours per day.

One (1) patient was able to create an air pocket over the implant caused by vigorous nose blowing. This was resolved through counseling.

One (1) patient developed a facial weakness two weeks post-surgery. This was treated with steroids and anti-inflammatory medication, and resolved prior to first-fitting.

Two (2) patients developed post-operative swelling at the implant site which decreased over time. One (1) was treated with the use of additional magnets to hold the external coil in place. The other wore a headband.

One (1) device case was reversed in the bone bed, resulting in the external coil magnet repelling rather than attracting. The patient received an external coil that was modified by reversing the coil magnet.

Device Related Adverse Events: Adults

Six (6) patients reported uncomfortable stimulation. Five (5) were resolved through reprogramming and exchange of external equipment. One (1) patient required a modified coil.

Two (2) patients reported a constant buzzing sound from the processor, one (1) of which experienced headaches and general discomfort.

One (1) patient reported a strong metallic taste sensation each time he stimulated the outer portion of his ear (example: water from shower in ear, finger touching ear canal).

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Two (2) patients reported tinnitus.

One (1) patient reported a two-week period of dizziness post-operatively.

Two (2) patients experienced probable facial nerve stimulation.

One (1) patient experienced a tickling sensation in the ear.

CHILDREN:

Nineteen (19) out of eighty-two (82) implanted children experienced nineteen (19) adverse events or complications. Three (3) were classified as major, requiring surgical intervention, [one (1) explantation and two (2) re-suturing], and sixteen (16) were classified as minor. All have been resolved.

Medical/Surgical Complications: Children

Two (2) patients presented with post-operative infection. They were treated with intravenous antibiotics and no further problems have been reported.

Three (3) patients presented with middle ear infections, which were resolved with medical treatment.

Three (3) patients' scalp incisions opened during the post-operative healing period. Two (2) of these required re-suturing. All incisions healed properly.

One (1) patient with a history of recurrent Acute Otitis Media (AOM) developed chronic otorrhea and granulation tissue. The patient was unsuccessfully treated with aggressive local management. The device has been explanted with subsequent re-implantation.

Two (2) patients had erythema at the implant site.

Device Related Adverse Events: Children

Three (3) children had facial nerve stimulation, which was resolved by programming.

Three (3) children had vertigo accompanied either by tinnitus or nausea.

One (1) child was only able to use five (5) stimulation channels.

One (1) child presented with skin irritation at the implant site as a result of continuing to wear a cracked coil.

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Potential Adverse Events: Adults and Children

In addition to the adverse events experienced during the clinical study, the following potential adverse events could occur:

Risks due to surgery
Cochlear implantation is subject to the same risks as other surgical procedures conducted under general anesthesia. In addition, surgery may result in loss of residual hearing in the implanted ear, facial nerve injury, taste disturbances, infection, incorrect device placement and pain at the site of the wound.

Potential side effects and medical complications
Cochlear implantation may result in a palpable lump behind the ear, numbness or stiffness in the area of the implant, leakage of perilymph fluid, tinnitus (ringing in the ear), vertigo (dizziness), risk of meningitis due to perilymph fluid leak, irritation, inflammation or breakdown of the skin with possible device extrusion.

Risks related to the device
Risks associated with implantation may include a device may not restore hearing to a level achieved by other cochlear implant users, facial stimulation and further degeneration in inner ear nerve cells. Long-term effects of stimulation of the hearing nerve with a cochlear implant are not fully known to date.

Device removal
Device removal may become necessary because of electrical or mechanical failure of the implant, an infection at the site of the surgical wound or at the site of the device that can not be successfully treated with medication; or because of migration of the device or the electrode carrier which may result in uncomfortably loud stimulation, no sound, or a reduction of the number of electrodes in use. There is a risk that removal of the cochlear implant may cause damage to the inner ear.

RESULTS OF THE US CLINICAL TRIAL

Study Population and Study Period:

ADULTS:

One-hundred and six (106) adults were implanted with the Implant C40+ standard electrode array at twenty-six (26) sites in the United States between November 10, 1997 and September 29, 2000. The cumulative experience was 713 months. Data from forty-five (45) post-lingually deafened and eighteen (18) pre-lingually deafened

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patients who have at least six (6) months device experience were used to support device efficacy. Thirty-five (35) patients have not been seen for the six (6) month follow-up, five (5) patients did not meet the inclusion criteria for the investigational protocol, and three (3) patients were exempted due to health issues or inability to comply with the protocol requirements.

CHILDREN:

Eighty-two (82) children were implanted with the Implant C40+ standard electrode array at eighteen (18) sites in the United States between April 1, 1998 and March 1, 2000. The cumulative implant experience was 553 months. Data from fifty-five (55) subjects who have at least six (6) months device experience were used to support device efficacy. Of these, thirty-four (34) were younger than five (5) years and twenty-one (21) were older than five (5) years of age. Eighteen (18) subjects had not reached the six (6) month follow-up, four (4) patients did not meet the inclusion criteria for the investigational protocol, and five (5) patients were exempted due to health issues or inability to comply with the protocol requirements.

SAFETY PROTOCOL:

In addition to the monitoring of all complications and adverse events, fifty (50) children and fifty (50) adults with a minimum of one (1) year device experience were used to evaluate device safety. These were comprised of fifty (50) US children, forty (40) US adults, and ten (10) European adults. The analysis for the fifty (50) US pediatric and forty (40) US adult patients was comprised of evaluating the stability of the threshold (THR) charges, the most comfortable level (MCL) charges and the dynamic range, the stability or increase of auditory perceptual measures over time, medical/otological evaluation, and monitoring of adverse events.

The safety data analysis for the ten (10) European adults consists of the evaluation of the stability of the threshold (THR) charges, and the most comfortable level (MCL) charges and dynamic range over time using initial stimulation (one (1) month), and post one (1) year data points.

Electrode Channel Activation

The following tables represent the number of electrode channels versus stimulation rate per channel for the COMBI 40+ clinical study adult and pediatric patients. Data displayed represents only those parameters selected by patients in the clinical trial.

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Adult: Evaluation 4 (6 months post initial fitting) N=38				
Stimulation Rate Per Channel in Pulses Per Second (PPS)				
Active Channels	**501-1250**	**1251-1750**	**1751-2500**	**2501-3500**
6				••
7	•			
8			•	
9	•		••••••	
10	•	•	•	
11	•	•		
12	•••••••	••••••• ••••••• •		

Pediatric: Evaluation 4 (6 months post initial fitting) N=49				
Stimulation Rate Per Channel in Pulses Per Second (PPS)				
Active Channels	**501-1250**	**1251-1750**	**1751-2500**	**2501-3500**
5				•
7		•	•	
8	•		•••	
9			••••	
10		•	•	
11		••••••		
12	•	••••••• ••••••• ••••••• ••••••• •		

As exhibited in the above tables, the investigational subjects received different rates of stimulation measured in pulses per second (PPS). For each participant the optimal stimulation rate per channel is displayed along the x-axis and the optimal number of active channels is displayed along the y-axis. The number of active channels affects the stimulation rate per channel. None of the patients selected programs with less than 5 channels, resulting in no programs with rates higher than 3,500 pps per channel.

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STUDY OUTCOMES AND STATISTICAL CONSIDERATIONS

ADULTS:

Device efficacy was defined as improved scores on speech recognition materials presented at conversational speech levels (70 dB SPL) in quiet in the auditory-only condition, as measured by the Hearing In Noise Test (HINT) sentence test. Device efficacy was evaluated using a single subject repeated measures design, with the subject serving as his/her own control. This method optimizes control over inherent variability among subject and disease characteristics. No attempt was made at blinding either the patients or the clinicians. Statistical analysis was performed on each speech recognition measure for all subjects comparing the best-aided pre-surgical condition to six (6) months experience with the COMBI 40+. Trends in impedance levels and fitting parameters, in addition to the monitoring of all adverse events, were analyzed to support device safety.

Sentence recognition materials presented using sound alone at normal conversational levels in quiet are considered to provide a standard clinical measure of everyday performance. It is generally agreed that an improvement as compared to the best-aided pre-surgical score of 20 percentage points on these materials represents a clinically significant increase in performance. Therefore, patients experiencing an increase of 20% or more on this measure were classified as exhibiting *clinically significant improvement.*

Many patients with poor open-set speech understanding derive clear subjective benefit in their daily lives from cochlear implantation. Therefore, patients demonstrating an increase on sentence recognition materials of less than 20% and an improvement in any other test are defined as *some improvement.*

Adult Data:

Data from forty-five (45) post-lingually deafened patients and eighteen (18) pre-lingually deafened patients with six (6) months device experience with the COMBI 40+ were used to substantiate device efficacy. The performance at six (6) months device experience was compared to the pre-operative best-aided hearing condition with appropriately fitted hearing aids.

The following tests were administered pre-operatively and at six (6) months device experience. All speech recognition tests were administered from CD recording at 70 dB SPL.

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• 4-choice spondee words	CD Recording
• Sentences in quiet	HINT sentences, CD recording City University of New York (CUNY) sentences, CD recording
• Sentences in noise	HINT sentences at 10dB SNR, CD Recording
• Monosyllabic words	Consonant-Nucleus-Consonant (CNC) words, CD recording
• Sentences via telephone	Central Institute for the Deaf (CID) sentences, live voice

Post-lingually Deafened Adults

The average age at implantation for the forty-five (45) post-lingually deafened patients was 53.5 years. These patients had a mean duration of hearing loss of twenty-eight (28) years.

At six (6) months experience with the COMBI 40+, post-lingual adults with hearing loss less than twenty-five (25) years (N=18) demonstrated:

- a mean increase in the ability to recognize words in CUNY sentences in quiet of 72% above their pre-operative score.
- a mean score of 86% on CUNY in quiet.
- a mean increase in the ability to recognize words in HINT sentences in quiet of 70% above their pre-operative score.
- a mean score of 75% on HINT scores in quiet.
- a mean increase in the ability to recognize words in HINT sentences in the presence of +10 dB SNR background noise of 61%.
- a mean score of 63% on HINT sentences in the presence of background noise.
- a mean increase in the ability to recognize CNC monosyllabic words of 40%.
- a mean score of 44% on CNC monosyllabic words.
- a mean increase in the ability to recognize CID sentences over the telephone of 68%.
- a mean score of 68% on CID sentences over the telephone.

At six (6) months experience with the COMBI 40+, post-lingual adults with hearing loss greater than twenty-five (25) years (N=27) demonstrated:

- a mean increase the ability to recognize words in CUNY sentences in quiet of 56% above their pre-operative score.
- a mean increase in the ability to recognize words in HINT sentences in quiet of 50% above their pre-operative score.

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- a mean increase in the ability to recognize words in HINT sentences in the presence of +10 dB SNR background noise of 41%.
- a mean increase in the ability to recognize CNC monosyllabic words of 29%.
- a mean increase in the ability to recognize CID sentences over the telephone of 42%.

Pre-lingually Deafened Adults

The average age at implantation for the eighteen (18) pre-lingually deafened patients was 37.4 years. These patients had a mean duration of hearing loss of 36.5 years. At six (6) months experience with the COMBI 40+, Pre-lingually Deafened adults, (N =18), range birth to 42[note 1] years, profoundly deafened prior to 6 years of age) demonstrated:

[note1] The upper limit of forty-two (42) years is for those cases when hearing loss was documented upon inclusion into the clinical trial. In all cases it has been found that these patients were deafened at birth, or prior to the age of six (6) due to maternal measles, maternal meningitis, or other congenital reasons.

- a mean increase in the ability to recognize words in CUNY sentences in quiet of 21% above their pre-operative score.
- a mean increase in the ability to recognize words in HINT sentences in quiet of 19% above their pre-operative score.
- a mean increase in the ability to recognize words in HINT sentences in the presence of +10 dB SNR background noise of 12%.
- a mean increase in the ability to recognize CNC monosyllabic words of 10%.
- a mean increase in the ability to recognize CID sentences over the telephone of 20%.

Length of Deafness Summary for Post-Lingually Deafened Adults

As a combined group (< twenty-five (25) years deafened (N=18) and > twenty-five (25) years deafened (N=27) populations), eighty-five (85) percent demonstrated clinically significant improvement defined as an increase on open set sentence tests of over 20% and all but one (1) demonstrated some improvement. When both recorded sentence tests included in the audiologic battery are considered (20% improvement on HINT in quiet or CUNY sentences), 91% of subjects achieved a 20% improvement on one or both of the test scores.

Following at least six (6) months of device usage, twenty-six (26) patients had the fitting of their TEMPO+ Speech Processor optimized with the DIB. After thirty (30) days with the new program, speech-understanding results on CUNY sentences in quiet and CNC words with the TEMPO+ Speech Processor were compared to the CIS PRO+ Speech Processor. Although the mean values for the TEMPO+ Speech

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Processor are higher than the CIS PRO+ Speech Processor, the difference was not statistically significant.

Eighty-four (84) percent of the subjects (N = 45) report that the implant has 'quite positively' (40%) or 'very positively' (44%) affected their lifestyle. Responses on the "Quality of Life" questionnaire demonstrated the following statistically significant improvements after six (6) months device experience as compared to the pre-operative condition:

- COMBI 40+ adult recipients are less concerned about their safety or welfare because of their deafness.
- They do not change their activities as much due to concerns about their safety of welfare because of their deafness.
- They are less often upset because they are deaf.
- Their deafness does not affect enjoyment of social events as much.
- They are more comfortable attending social events.
- They feel less isolated as a result of their deafness.
- Their deafness does not affect their sense of belonging as much.
- They find it easier to visit a store or restaurant alone.
- It is easier for them to communicate.
- It is less frustrating for them to communicate.
- The quality of their closest relationship is less affected by their deafness.
- They do not feel left out of conversations with family members as much.
- Their relationships with friends are more satisfying.
- Their relationships with friends are less affected by their deafness.
- Their performance at work was less affected by their deafness.
- Deafness did not alter their hobbies or recreational activities as much.
- They more often engaged in activities that usually require hearing (watching TV, attending sporting events).
- Their lifestyle is less affected by their deafness.

Although most of the instrument items do not demonstrate statistically significant improvements in quality of life for the pre-lingually deafened patients, probably due to limited power related to the small sample, responses to most of the items are more favorable at six (6) month post implant as compared to pre-surgical. After six (6) months of experience with the Implant C40+, 83% of these subjects (N = 18) reported that the device 'very positively' (50%) or 'quite positively' (33%) affected their lifestyle.

CHILDREN:

Device efficacy was defined as improved performance on any measure of the speech perception battery in quiet after six (6) months of device use as compared to the best-aided pre-surgical condition on age-appropriate measures. Because children express improvement in speech recognition differently due to age,

maturation, language and cognitive development, a different test battery was used for younger children (ages eighteen (18) months through four (4) years eleven (11) months) than for older children (ages five (5) years through seventeen (17) years eleven (11) months). In addition to speech perception measures, the Meaningful Auditory Integration Scale (MAIS) and the Infant Toddler Meaningful Auditory Integration Scale (IT-MAIS) was administered as a measure of the child's ability to integrate auditory information into daily routines, enabling evaluation of children who have difficulty taking standardized tests due to maturational factors. Sound-field warble tone, speech detection and speech recognition thresholds were measured to complement the assessment of auditory performance. An auditory skills checklist was also administered and evaluated. Clinical safety was supported by monitoring of all adverse events and analysis of stability of electrode impedances, fitting parameters and auditory perceptual measures over time.

The primary measure of efficacy is a single test of binomial proportions to test that the Med-El COMBI 40+ Cochlear Implant System improved performance on any measure of the speech perception battery in quiet after six (6) months of device use compared to the best-aided pre-surgical condition on age-appropriate measures. As a secondary set of analyses, group scores are compared using a Student's Paired t-Test for each audiologic measure at pre-surgical compared with the six (6) month evaluation. In addition, poolability of data across investigational sites and audiological performance over time are analyzed using repeated measures analysis of variance (RM-ANOVA) models, including terms for investigational site and time in the statistical models. Due to the multiplicity of assessments (i.e., 10 in older children, 5 in younger children), statistical significance of the primary analysis of the single test of proportions test is considered 0.05 / 10 = 0.005 for older children, and 0.05 / 5 = 0.01 for younger children. A two-sided alpha level of 0.05 is considered statistical significant for all statistical hypothesis tests in the secondary analyses. Descriptive statistics are supplied for each test according to the age group to fully characterize the outcome of all the study participants.

Younger children:

Children who enter the study as a member of this age category (ages eighteen (18) months through four (4) years eleven (11) months) continued with the same protocol throughout the study even if they exceeded the age of five (5) during the follow-up period. The mean age for this group was 2.9 years.

All of the following test measures were administered pre-operatively and at six (6) months device experience with the COMBI 40+ for the younger children who were capable of taking the tests. All live-voice test administration was monitored with a sound-level meter at 70 dB SPL. All recorded tests were administered at 70 dB SPL.

- IT-MAIS Parent Interview.

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- Early Speech Perception (ESP) test Low Verbal Version administered live-voice.

- Glendonald Auditory Screening Procedure (GASP) Words administered live voice. The GASP could not be administered immediately following the ESP standard pattern perception subtest because of shared vocabulary.

- Auditory Skills Checklist was completed by the child's therapist (must have been a certified audiologist, speech language pathologist, or auditory-verbal therapist).

Of the younger children who were capable of being tested on open-set word recognition tasks:

- 70 % (16/23) demonstrated improvement on the ESP low verbal pattern perception test.
- 50 % (10/20) demonstrated improvement on the ESP low verbal spondee identification test.
- 48 % (10/21) demonstrated improvement on the ESP low verbal monosyllabic word identification test.
- 57 % (12/21) demonstrated improvement on the GASP open set word test.

IT-MAIS parental questionnaire:

- All younger children who were tested (33/33) improved on the IT-MAIS as an overall score.
- As a group, the younger children significantly improved on all questions of the IT-MAIS:
    - 76% (25/33) of the children frequently or always responded to their name in quiet compared with 15% (5/33) pre-operatively.
    - 52% (17/33) of the children frequently or always responded to their name in noise compared with 3% (1/33) pre-operatively.
    - 67% (22/33) of the children frequently or always spontaneously alerted to environmental sounds compared with 6% (2/33) pre-operatively.
    - 45% (15/33) of the children frequently or always alerted to new sounds when in an unfamiliar surrounding compared with 0% (0/33) pre-operatively.
    - 67% (22/33) of the children frequently or always recognized or responded appropriately to sounds in the classroom and at home compared with 3% (1/33) pre-operatively.
    - 52% (17/33) of the children frequently or always were able to discriminate between two speakers using audition alone compared with 6% (2/33) pre-operatively.

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- 67% (22/33) of the children frequently or always recognize speech as different than non-speech sounds compared with 6% (2/33) pre-operatively.
- 55% (18/33) of the children frequently or always were able to associate vocal tone (anger, excitement) with its meaning as compared to 12% (4/33) pre-operatively.

Older Children:

Children aged five (5) years through seventeen (17) years eleven (11) months. Children in this group had a mean age at implantation of 8.8 years.

All of the following test measures were administered pre-operatively and at six (6) months device experience with the COMBI 40+ for the older children who were capable of taking the tests. All live-voice test administration was monitored with a sound-level meter at 70 dB SPL. All recorded tests were administered at 70 dB SPL. The following measures have been used to establish device efficacy:

- MAIS Parent Interview
- ESP Standard Version administered live voice
- Multisyllabic Lexical Neighborhood Test (MLNT), Level 1 recorded version
- Lexical Neighborhood Test (LNT), Level 1 recorded version
- GASP Words administered live voice
- Bamford-Kowal-Bench (BKB) Sentences recorded version
- Auditory Skills Checklist to be completed by the child's therapist (must have been a certified audiologist, speech language pathologist, or auditory-verbal therapist).

Of the older children who were capable of being tested on open-set word recognition tasks:

- 68% (13/19) demonstrated improvement on the ESP standard pattern perception test.
- 79% (15/19) demonstrated improvement on the ESP standard spondee identification test.
- 68% (13/19) demonstrated improvement on the ESP standard monosyllabic word identification test.
- 79% (15/19) demonstrated improvement on the GASP open set word test.

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- 63% (12/19) demonstrated improvement on the LNT word test.
- 89% (17/19) demonstrated improvement on the LNT phonemes test.
- 65% (11/17) demonstrated improvement on the MLNT words test.
- 82% (14/17) demonstrated improvement on the MLNT phonemes test.
- 53% (10/19) demonstrated improvement on the BKB sentence test.

MAIS parental questionnaire:

- All older children who were tested (20/20) improved on the MAIS as an overall score.
- As a group, the older children significantly improved on all questions of the MAIS:
    - 95% (19/20) of the children frequently or always responded to their name in quiet compared with 55% (11/20) pre-operatively.
    - 80% (16/20) of the children frequently or always responded to their name in noise compared with 25% (5/20) pre-operatively.
    - 80% (16/20) of the children frequently or always spontaneously alert to environmental sounds in the home compared with 25% (5/20) pre-operatively.
    - 70% (14/20) of the children frequently or always alerted to new sounds when in an unfamiliar surrounding compared with 25% (5/20) pre-operatively.
    - 75% (15/20) of the children frequently or always responded recognized or responded appropriately to sounds in the classroom and at home compared with 45% (9/20) pre-operatively.
    - 65% (13/20) of the children frequently or always were able to discriminate between two speakers using audition alone compared with 40% (8/20) pre-operatively.
    - 70% (14/20) of the children frequently or always recognize speech as different than non-speech sounds compared with 45% (9/20) pre-operatively.
    - 55% (11/20) of the children frequently or always were able to associate vocal tone (anger, excitement) with its meaning as compared to 25% (5/20) pre-operatively.

Communicative Skills Checklist (older and younger children):

The terms "sometimes", "often" and "always" refer to responses at the 25%, 50% and 75%+ level, respectively.

- 84% (42/50) of the children often or always searched for the sound source compared to 34% (17/50) pre-operatively.

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- 80% (40/50) of the children often or always identified a sound source compared to 34% (17/50) pre-operatively.
- 62% (31/50) of the children were able to discriminate intensity differences often or always compared to 36% (18/50) pre-operatively.
- 80% (40/50) of the children were able to discriminate durational cues often or always compared to 50% (25/50) pre-operatively.
- 68% (34/50) of the children were able to discriminate pitch differences often or always compared to 28% (14/50) pre-operatively.
- 76% (38/50) of the children were able to respond to sounds at a distance often or always compared to 22% (11/50) pre-operatively.
- 72% (36/50) of the children were often or always able to associate a familiar sound with its meaning or anticipated event compared to 26% (13/50) pre-operatively.
- 64% (32/50) of the children were often or always able to improve their speech.
- 56% (28/50) of the children were able to respond to simple directions often or always using audition alone compared to 26% (13/50) pre-operatively.
- 36% (18/50) of the children were often or always able to identify and comprehend speech in a noisy environment without lip reading compared to 8% (4/50) pre-operatively.
- 24% (12/50) of the children were able to understand a message from an electronic sound source such as radio or film compared to 6% (3/50) pre-operatively.

Patient Counseling Information:

Prospective cochlear implant patients must be properly counseled prior to surgery, and expectations must be realistic. Information for prospective patients is available upon request from MED-EL. Expected performance with the cochlear implant cannot be accurately predicted. Duration of deafness, age at implantation, primary communication mode, communicative ability and the patient's auditory environment all have an impact on success with the cochlear implant. There may be other unknown factors, which also mitigate success with an implant. The professionals at a cochlear implant center are the best source of information regarding the expected outcome following implantation. It is also imperative that the patient and/or parents fully understand the risks associated with the procedure and the requirements for long-term follow-up care.

The final decision on ear selection remains at the discretion of each clinic. However, the ear with the least obstruction to full electrode insertion should be considered.

Pre-lingually deafened adults may not demonstrate the same degree of benefit as post-lingually deafened adults. There is potential for awareness and recognition of environmental sounds, enhanced lip-reading capabilities, improvement in voice

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monitoring and speech production and in some instances the ability to understand speech without lip-reading.

Pre-lingually deafened adult patients should be counseled regarding the limited benefit that they may receive from cochlear implantation. These patients must be highly motivated because they tend to be more likely to discontinue cochlear implant use.

STERILIZATION AND SHELF LIFE:

The Implant C40+ has been exposed to a validated Ethylene Oxide (EO) sterilization cycle and is delivered in a sterile package. It has a shelf life of at least two (2) years. If the expiration date marked on the package has expired, the device must be returned to the manufacturer for possible re-sterilization before being implanted.

Please note that the implant is double-packaged in two (2) transparent packages. Examine the sterile packages to make sure that the welded seams are intact. If the seams are not intact, or if you suspect that sterility has otherwise been compromised, the implant should not be used.

STORAGE AND HANDLING:

Unused Implants C40+ should be stored in the outer transportation carton at normal humidity and temperature in the range of 50°F - 80°F. Avoid temperature extremes below 32°F or above109°F.

EXERCISE CAUTION AT ALL TIMES WHILE HANDLING THE STERILE PACKAGE, OPENING THE PACKAGE, OR HANDLING THE IMPLANT! Do not implant a device that has been dropped. Return it to the manufacturer for replacement, and use a backup device instead.
Please note that the implant contains a high intensity magnet within the ceramic housing.

TO OPEN THE STERILE PACKAGE PLEASE USE THE FOLLOWING PROCEDURE (PLEASE CHECK LABELING FOR PACKAGE CONTENT):

- Do not use the implant if the packaging is damaged.
- Do not open package until needed during surgery.
- Caution – Do not drop!
- Caution – Implant is magnetic!
- Contaminated, non-sterile implants cannot be re-sterilized.

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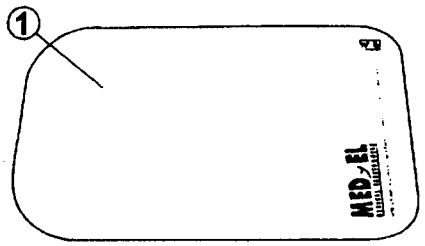
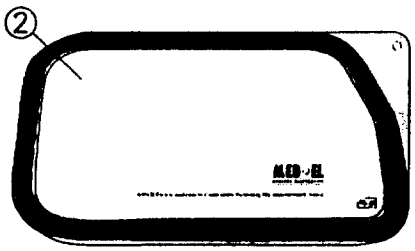
The sterile Implant package consists of:

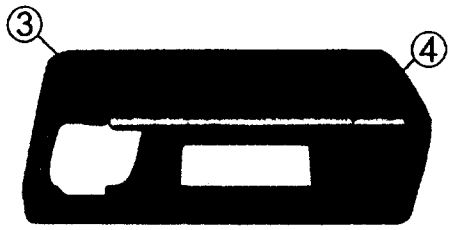
1 outer package with sealed Tyvek lid (1)



1 inner package with sealed Tyvek lid (2)



1 implant holding tray (3)
1 plastic tube (4) (electrode protection)



Both packages are opened by peeling off the Tyvek Lid (see labeling: "Open here")

STEP 1: HOW TO OPEN THE OUTER PACKAGING

- Check labeling for package content and peel off and dispose of the Tyvek lid.

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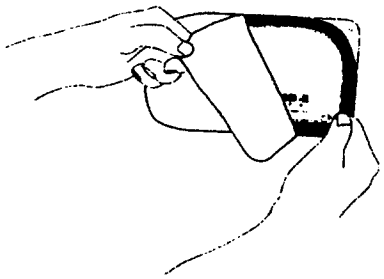
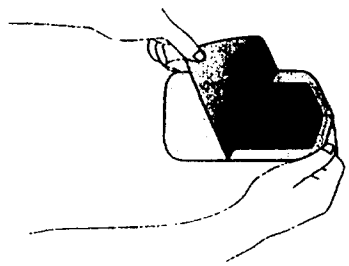


- Place one hand over the inner packaging and turn the packaging over (upper part down).

- Remove and dispose of the outer packaging (transparent).

STEP 2: HOW TO OPEN THE INNER PACKAGING

- Peel off and dispose of the Tyvek lid.



- Place one hand over the black-tinted Implant holding tray and turn the packaging over (upper side down).
- Gently squeeze the Implant holding tray out of its packaging onto a flat surface.

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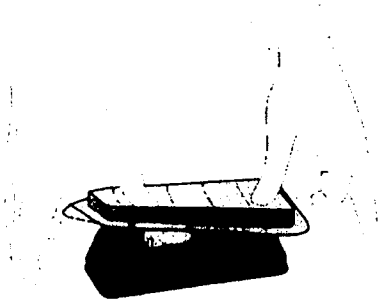
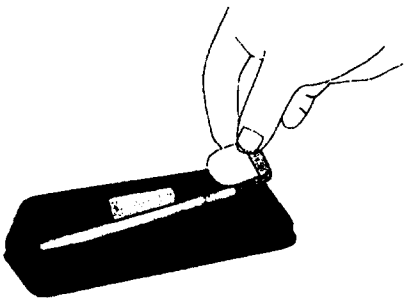
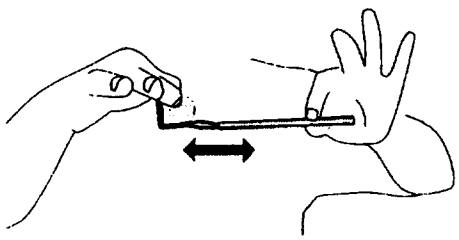


- Dispose of the inner packaging (transparent).
- Hold the implant at the finger access and horizontally pull the electrode out of the protective plastic tube.





- Dispose of the implant holding tray (black-tinted) and the plastic tube.

Never lift, hold, suspend or carry the Implant C40+ by the electrode! This may result in unseen damage to the electrode contacts or the leads within the electrode, and cause complete device failure. Hold the Implant C40+ by the ceramic body only.

Use only the Surgical Templates when fitting and measuring for the position of the implant and electrodes on the patient's skull. Handle the electrode only with the surgical instruments provided in the Surgical Kit. Place the actual implant only when certain that it will not need to be replaced or re-positioned.

Caution: Federal (US) law restricts this device to sale, distribution and use by or on the order of a physician.

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USER MANUAL FOR THE
MED-EL TEMPO+
EAR LEVEL SPEECH PROCESSOR

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