Synthes Spine

DRAFT PACKAGE INSET

IMPORTANT INFORMATION ON THE SYNTHES VERTICAL EXPANDABLE PROSTHETIC TITANIUM RIB SYSTEM

4/04 **GPxxxx-A, Rev1**

IMPORTANT: Prior to use, the physician should be trained in the surgical procedure recommended for the use of this device.

Humanitarian Device: The Vertebral Expandable Prosthetic Titanium Rib (VEPTR) is authorized by Federal law for use in the treatment of Thoracic Insufficiency Syndrome, the inability of the thorax to support normal respiration or lung growth, in skeletally immature patients. The effectiveness of this device for this use has not been demonstrated.

CAUTION: U.S. federal law restricts this device to sale by or on the order of physician with appropriate training or experience.

INDICATIONS FOR USE

The VEPTR is indicated for treatment of Thoracic Insufficiency Syndrome in skeletally immature patients. Thoracic Insufficiency Syndrome is defined as the inability of the thorax to support normal respiration or lung growth. Thoracic Insufficiency Syndrome is considered to be a rare condition.

For the purpose of identifying potential Thoracic Insufficiency Syndrome patients, the categories in which Thoracic Insufficiency Syndrome patients often fall are as follows:

- Flail Chest Syndrome
- Rib fusion and scoliosis
- Hypoplastic thorax syndrome, including, but not limited to:
  - Jeune's syndrome
  - Achondroplasia
  - Jarcho-Levin syndrome
  - Ellis van Creveld syndrome

DESCRIPTION

The VEPTR devices are attached perpendicularly to the subject's natural ribs and lumbar vertebra or hip. This mechanically stabilizes the chest wall and enlarges the thorax to improve respiration and lung growth. Once the VEPTR is in place, its design allows for expansion, anatomic distraction, and replacement of component parts through less

invasive surgery. The VEPTR device is comprised of a combination of the following titanium component(s):

- Superior Cradle
- Inferior Cradle
- Cradle End Half
- Extended Cradle End Half
- Rib Sleeve
- Cradle Lock
- Distraction Lock
- Lumbar Extension
- Low Profile Lamina Hook
- Sacra Ala Hook
- Connector
- 2mm Ti Rod

The VEPTR is available for assembly in three configurations

- Cradle to Cradle
- Cradle with Lumbar Extension
- Cradle to Ala Hook

The Cradle to Cradle Assembly is available in two different radii (approximately 220mm radius and 70mm radius of curvature) and various lengths. The other two assemblies are available in 220mm radius only. The semicircular end of the inferior and superior cradles are provided in different angles (0°, 30° right, and 30° left) to accommodate subject anatomy, and are connected to the cradle end half by a cradle lock. These portions of the construct encase the natural rib(s). The cross-sections of the proximal ends of the rib cradles are "T-shaped" for enhanced strength. The superior cradle and inferior cradle/lumbar extension attach to the rib sleeve by inserting a distraction lock at each end. The rib sleeve is the central section of the construct. The rib sleeve serves as a track into which the cradles slide. A through hole in the rib sleeve is aligned with one of the blind holes on the superior and inferior cradle. The distraction locks are inserted into aligned sets to holes at both ends of the construct. The position of the inferior cradle assembly along the rib sleeve depends on the desired length of the overall rib prosthesis construct. All of these configurations are required to accommodate the wide variety of anatomical deformities encountered by the clinician in treating Thoracic Insufficiency Syndrome patients.

Cradle to Cradle Assembly

The Cradle to Cradle Assembly consists of 9 pieces: a superior cradle, an inferior cradle, a rib sleeve, two cradle end halves, two cradle locks and two distraction locks. These assemblies are available in 70mm and 220mm radii versions. The Cradle to Cradle

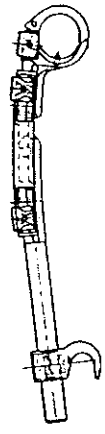
Assembly is normally used when the patient has Thoracic Insufficiency Syndrome due to fused/missing ribs, severe scoliosis, and/or hypoplastic thorax.

Cradle to Cradle Assembly
70 mm Radius

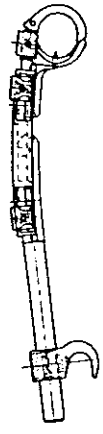
Cradle to Cradle Assembly
220 mm Radius

Cradle with Lumbar Extension Assembly

The Cradle with Lumbar Extension Assembly consists of 8 pieces: a superior cradle, a rib sleeve, a lumbar extension, a cradle end half, a cradle lock, two distraction locks and a low profile lamina hook. This is available in the 220mm radius version only. The Cradle with Lumbar Extension Assembly is indicated for use where no lower ribs exist or when the scoliotic curve extends into the lumbar region of the spine.



Lumbar
220mm



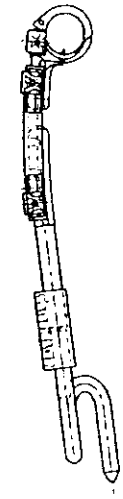
Extension Assembly
Radius Only

Cradle to Ala Hook Assembly

The Cradle to Ala Hook Assembly consists of 9 pieces: a superior cradle, a rib sleeve, a lumbar extension, a cradle end half, a cradle lock, two distraction locks, an extension connector and an ala hook. The assembly is available in 220mm radius only. The Cradle

to Ala Hook Assembly is indicated for use when attachment of the lower portion of the assembly to the hip is necessary.

Ala Hook Assembly
220mm Radius Only



The superior and inferior cradles are available in 0 degree, 30 degree right and 30 degree left configurations to suit the anatomy. The inferior cradles and rib sleeves come in 10 lengths for the 220mm radius version and 8 lengths for the 70mm radius version. The lumbar extensions are available in 8 lengths to allow for anatomical variations and device expansion to accommodate patient growth. The ala hooks and the low profile lamina hooks are available in left and right hand versions to allow placement on the appropriate side of the spine. The cradle end half is available in two configurations: 1) the standard version which is capable of capturing 1 rib and 2) the extended version which can capture 2 or more ribs.

All components are manufactured from titanium alloy, Ti-6Al-7Nb (ASTM F1295), with the exception of the sacral ala hook and 2mm rod, which are manufactured from commercially pure titanium, TiCP4 and TiCP1, (ASTM F67), respectively. These materials have a long history of safe use as an implantable material.

Associated manual instrumentation utilized for the implantation of these components is available for the distraction, insertion, expansion and removal of the VEPTR.

CONTRAINDICATIONS

The VEPTR device should not be used under the following conditions:

- Inadequate strength of bone (ribs/spine) for attachment of the VEPTR
- Absence of proximal and distal ribs for attachment of the VEPTR
- Absent diaphragmatic function
- Inadequate soft tissue for coverage of the VEPTR

- Age beyond skeletal maturity for uses of the VEPTR
- Age below 6 months
- Known allergy to any of the device materials
- Infection at the operative site

WARNINGS AND PRECAUTIONS

Humanitarian Device: Authorized by Federal law for use in the treatment of Thoracic Insufficiency Syndrome in skeletally immature patients. The effectiveness of this device has not been demonstrated.

Patients implanted with the VEPTR should not be braced. The VEPTR device is designed to allow for thoracic cavity growth and the restrictive nature of a brace would not help the condition, but defeat its purpose.

Patients may require additional wound protection to prevent inadvertent rubbing or bumping of the wound.

Patients with a diagnosis of spina bifida should have an occlusive dressing over the wound site to keep the site dry.

ADVERSE EFFECTS OF THE DEVICE ON HEALTH

OBSERVED ADVERSE EVENTS

Adverse effects were reported on the study Case Report Form (CRF) or directly to Synthes by telephone or monitoring report in advance of completion of the CRF. This application contains all adverse effects known to Synthes, from the time the device was first implanted in April 1989 to July 2003.

Treatment-emergent events were reported for the entire length of study follow-up (mean follow-up for the feasibility study was 84.8 months, mean follow-up for the multicenter study was 22.6 months). A total of 29 (88%) of 33 patients reported a total of 182 adverse effects while a total of 68 adverse effects considered to be related to the device were reported in 21 (64%) patients. Eleven (11) adverse effects of life-threatening intensity were reported for 2 patients and 13 adverse effects of fatal intensity were reported for 4 patients. These adverse effects were not considered to be device-related by the investigators.

A total of 119 (56%) of 214 patients in the multicenter study reported a total of 356 adverse effects while a total of 141 adverse effects considered to be related to the device were reported in 71 (33%) patients. Twelve (12) adverse effects of life-threatening intensity were reported for 9 patients and 16 adverse effects of fatal intensity were reported for 8 patients. These adverse effects were not considered to be device-related by the investigators.

Most of the device related adverse effects were device migrations. Device migrations included asymptomatic migrations through the proximal ribs, hook migrations distally through the vertebral lamina and also includes dislodgements of the spinal hooks. The migration is a localized "disattachment" from bony points of attachment to the spine or proximal ribs and not a migration inside the chest. Many of the device migrations occurred after subjects had been implanted with the VEPTR for two or more years.

SUMMARY OF CLINICAL INVESTIGATIONS

Objective

A prospective, multi-center clinical trial of the VEPTR device was conducted in the United States to determine the safety and effectiveness of the device in the treatment of TIS. All patients enrolled into the study were treated with the VEPTR device and served as their own controls.

Inclusion and Exclusion Criteria

Eligible patients had a primary diagnosis of TIS with a thorocodorsal malformation classified in one of the following categories:

Category I: Flail Chest Syndrome, including congenital chest wall defect, acquired surgical chest wall deficit due to tumor resection, surgical separation of conjoined twins, traumatic flail chest.

Category II: Congenital Constrictive Chest Wall Syndrome, including rib fusion or hypoplastic thorax syndrome; rib fusion with progressive thoracic scoliosis without vertebral anomalies; rib fusion with secondary chest wall constriction by progressive thoracic congenital scoliosis; hypoplastic thorax syndrome; Jeune's syndrome (asphyxiating thoracic dystrophy); achondroplasia; Jarcho-Levin syndrome (lethal autosomal short-trunk dwarfism); Ellis van Creveld syndrome (chondroectodermal dysplasia).

Category III: Progressive spinal deformity (scoliosis or kyphosis) without rib anomaly, e.g., progressive scoliosis of neurogenic or congenital origin.

Patients were 6 months of age or older, up to the age of skeletal maturity, depending on the diagnostic category.

Clinical Trial Design

This was a prospective, single-treatment arm study conducted in two phases: a single investigational site feasibility study and a multi-center pivotal trial.

Patient Population and Demographics

A single site feasibility study with thirty three (33) patients and a multi-center, prospective study at seven (7) sites with two hundred twenty four (224) patients were performed. A total of two hundred fifty seven (257) patients were studied, but ten (10)

patients were excluded from the analysis due to the absence of baseline data. Enrolled patients at each site received the VEPTR device assembly according to disease pathology and anatomical requirements. For the purposes of reporting the results, the study population was divided into four diagnostic categories: Flail Chest, Rib Fusion, Hypoplastic Thoracic Syndrome, and Progressive Scoliosis.

Table 1
Study Population

Study Phase	Diagnostic Category				Total
	Flail Chest	Rib Fusion	Hypoplastic Thoracic Syndrome	Progressive Scoliosis	
Feasibility	6	19	6	2	33
Multi-Center	8	75	87	44	214
Totals	14	94	93	46	247

Table 2
Patient Demographics
Feasibility and Multi-Center Studies

	Diagnostic Category				Total
	Flail Chest	Rib Fusion	Hypoplastic Thoracic Syndrome	Progressive Scoliosis	
N	14	94	93	46	247
Male (%)	8 (57.1%)	49 (52.1%)	43 (46.2%)	24 (52.2%)	124 (50.2%)
Female (%)	6 (42.9%)	45 (47.9%)	50 (53.8%)	22 (47.8%)	123 (49.8%)
Age, mean (years)	5.1	3.7	3.3	5.2	3.9
Age range (years)	0.0-15.0	0.0-14.0	0.0-15.0	0.0-12.0	0.0-15.0

Evaluation Schedule

Clinical examinations were performed at each surgical procedure and at the post-operative follow-up visits at 4 months (±2 months), 8 months (±2 months), 12 months (±2 months), 16 months (±2 months), 20 months (±2 months), 24 months (±4 months), and annually thereafter (±4 months). At each follow-up visit, patients had general physical examinations, measurements of sitting and standing height, chest and abdominal circumference (inspiration and expiration), vital signs, weight, Assisted Ventilation Rating (AVR) (an outcome measure specifically developed for this investigation), Quality of Life Assessment (QOL) (Child Health Questionnaire for children ≥5 years, or Infant/Toddler Health Questionnaire for children <5 years), capillary blood gases, oxygen saturation (pulse oximeter), pulmonary function tests (in children >7 years without

developmental delay), and radiographs (for measurements of thoracic dimensions and Cobb angles).

As the patients experienced normal growth and/or as the spine and thorax required further correction, the study device would require expansions or replacement of the components to increase the overall size of the device. As a guideline, children with scoliosis or flail chest syndrome were to be scheduled for expansion of the device when the Cobb angle increased by 5˚or greater. Children with hypoplastic thoracic syndrome were to be scheduled for device expansion approximately every 6 months.

Surgical Procedures

After the initial VEPTR surgical procedure, patients were expected to undergo multiple surgical procedures to expand, replace and remove the VEPTR as part of the normal course of treatment in order to further correct chest wall deformities and accommodate for growth. For the 214 Multi-Center patients, there were 1,051 follow-up surgical procedures, an average of nearly 5 follow-up surgeries per patient. Approximately 75% of these subsequent surgeries were device expansions.

Table 3
Follow-Up Surgical Procedures
(% of patients)

	Diagnostic Category				Total
	Flail Chest	Rib Fusion	Hypoplastic Thoracic Syndrome	Progressive Scoliosis	
Multi-Center, n	8	75	87	44	214
Total procedures (%)	26	339	592	94	1051
Expansion (%)	19 (73.1)	253 (74.6)	442 (74.7)	71 (75.5)	785 (74.7)
Replacement (%)	0	49 (14.5)	78 (13.2)	14 (14.9)	141 (13.4)
Removal (%)	3 (11.5)	9 (2.7)	2 (0.3)	2 (2.1)	16 (1.5)
Other (%)*	4 (15.4)	28 (8.3)	70 (11.8)	7 (7.4)	109 (10.4)

* Other surgical procedures include device re-seating or repositioning, partial or total removals, revision of components, and implantation of extensions or additional components, wound debridements, drainages, delayed wound closures, incision and drainages, and dressing changes, non-orthopedic procedures including aspiration of pleural effusions, lymph node biopsies, suture removals, tracheotomy closure, laryngoscopy, Porta Cath insertion, inguinal hernia repair, pulmonary lobectomy, bronchoscopy, and gastric tube replacement procedures.

Patient Accountability

There were 33 patients enrolled in the feasibility study and 224 patients enrolled in the multi-center study. Data from ten patients were not available at the time of database closure and were not included in the analysis. Thus, 214 patients from the multi-center study were analyzed.

Of the 247 patients enrolled in either study, 12 patients died and 2 patients withdrew, leaving 233 patients. Within one year of database closure, 215 patients had evaluations, 5 were lost to follow-up, 5 were seen at other study sites after database closure, 3 were seen at an IRB-suspended site, 3 did not require further surgery, 1 lived in New Zealand, and 1 was transferred to another site.

For the feasibility study, the 2-year, 3-year, and 5-year follow-up rates for those time points or greater were 93.5%, 96.6%, and 89.7%, respectively, and for the multi-center study, 85.7%, 95.8%, and 95.0%, respectively.

Effectiveness Data

- **Assisted Ventilatory Rating (AVR) Outcomes**

Standard pulmonary function test measurements, such as *forced expiratory volume* (FEV), *maximal voluntary ventilation* (MVV), *residual volume* (RV), and *total lung capacity* (TLC), were not feasible in this population because most patients were less than 7 years old and/or developmentally delayed and were unable to follow directions required for these tests. Therefore, the Assisted Ventilatory Rating (AVR) was used to assess treatment effectiveness. AVR outcomes were determined relative to preoperative baseline score. AVR scores were defined as follows:

+0: room air
+1: supplemental oxygen
+2: night ventilation
+3: part-time ventilation or CPAP
+4: full-time ventilation

The AVR outcomes demonstrated improvement or stabilization in 84.4% of patients for the feasibility study and 93.4% of patients for the multi-center study, or 92.0% of patients overall. Each of the diagnostic categories demonstrated improvement or stabilization AVR outcomes.

Table 4
AVR Outcomes

	Diagnostic Category				Total
	Flail Chest	Rib Fusion	Hypoplastic Thoracic Syndrome	Progressive Scoliosis	
Feasibility	3 (50.0)	17 (94.4)	5 (83.3)	2 (100.0)	27 (84.4)
Multi-Center	7 (100.0)	62 (92.5)	71 (91.0)	29 (100.0)	169

					(93.4)
Combined	10 (76.9)	79 (92.9)	76 (90.5)	31 (100.0)	196 (92.0)

- **Thoracic dimensions**

The goal of treatment with VEPTR was to equilibrate the height of each individual hemithorax and maintain this correction with each expansion of the devices. Table 5 shows the number and percentage of the subjects who met this goal of treatment, allowing growth of the thoracic spine and increase in the hemithoracic height and volume.

- **Cobb Angle**

The Cobb angle is a measurement of the patient's spinal curvature. A decrease in Cobb angle represents an improvement. For this study, maintenance was defined as stabilization (±5 degree change from baseline) or improvement (>5 degree reduction from baseline) of the Cobb angle. The Cobb Angle outcomes for this study ranged from are noted in Table 5.

Table 5
Device Outcomes

	Flail Chest	**Rib Fusion**	**Hypoplastic Thoracic Syndrome**	**Progressive Scoliosis**
Multi-Center, n	8	75	87	44
Thoracic Ht Outcomes	4 (80.0)	54 (91.5)	56 (84.8)	24 (77.4)
Hemithoracic Ht (Initial Side) Outcomes	4 (80.0)	50 (86.2)	58 (90.6)	23 (88.5)
Hemithoracic (Secondary Side) Ht Outcomes	3 (60.0)	42 (72.4)	52 (80.0)	16 (59.3)
Hemithoracic Width (Initial Side) Outcomes	3 (60.0)	48 (81.4)	54 (83.1)	20 (74.1)
Hemithoracic Width (Secondary Side) Outcomes	4 (80.0)	45 (76.3)	53 (81.5)	15 (53.6)
Cobb Angle Outcomes	5 (100.0)	51 (83.6)	47 (73.4)	24 (80.0)

Safety Analysis

Twenty-nine of 33 patients in the feasibility study had 408 adverse effects, while 119 of 214 patients (56%) in the multicenter study had 1,051 adverse effects. Respiratory problems such as pneumonia and dyspnea and other conditions, such as fevers, were frequently encountered during the study. These adverse effects are categorized into the following groups:

Table 6
Adverse Events

	Feasibility		Multi-Center	
	Events[1]	Patients[2]	Events[1]	Patients[2]
	408	33	1051	214
Device-Specific	37	16 (48%)	52	34 (16%)
-Device Migration	25	14 (42%)	49	34 (16%)
-Device Failure	13	7 (21%)	6	5 (2%)
-Device Other	1	1 (3%)		
Body as a Whole	9	5 (15%)	47	29 (14%)
-Abscess	1	1 (3%)	13	8 (4%)
-Infection	4	2 (6%)	11	10 (5%)
-Infection, bacterial			4	4 (2%)
-Infection, fungal			2	2 (1%)
-Pain			6	5 (2%)
-Cellulitis	1	1 (3%)		
-Pain, headache	1	1 (3%)		
-Pain, back	1	1 (3%)	2	2 (1%)
-Pain, chest			1	1 (0%)
-Pain, neck			1	1 (0%)
-Fever	1	1 (3%)	3	3 (1%)
-Injury			3	3 (1%)
-Necrosis			1	1 (0%)
Respiratory			16	11 (5%)
-Pneumonia			6	6 (3%)
-Effusion			3	3 (1%)
-Pneumothorax			3	3 (1%)
-Atelectasis			1	1 (0%)
-Respiratory Disorder			1	1 (0%)
-Respiratory Distress Syndrome			1	1 (0%)
-Acidosis, respiratory			1	1 (0%)
Skin and Appendages			13	7 (3%)
-Dermatitis			11	5 (2%)
-Healing, abnormal			1	1 (0%)
-Rash, vesicular			1	1 (0%)
-Injury, accidental	1	1 (3%)		
Metabolic and Nutritional	5	3 (9%)	4	4 (2%)
-Healing, abnormal	5	3 (9%)	4	4 (2%)

Nervous			4	3 (1%)
-Neuropathy	1	1 (3%)		
-Transient Spinal Cord	1	1 (3%)		
-Convulsion			1	1 (0%)
-Hypokinesis			1	1 (0%)
Urogenital	1	1 (3%)		
-Infection, urinary tract	1	1 (3%)		

1 Number of individual adverse events
2 Number of patients experiencing an adverse event

There were 4 intraoperative complications reported for the feasibility and multi-center studies (1.9% of all patients), including a technical error in device placement; a dural laceration, and pressure on the brachial nerve. Sixteen feasibility patients, or 48%, experienced 37 device-specific adverse events, and 34 multi-center patients, or 16%, experienced 52 device-specific adverse events. These device-specific adverse events included device fractures, device migrations, and other device-related adverse events. Device migrations occurred frequently—25 migrations in the feasibility study and 49 migrations in the multi-center study. They were more common with the cradle-to-lumbar extension and cradle-to-sacral ala because these two configurations undergo greater flexion, extension, rotation and lateral bending forces. The cradle to cradle assemblies are primarily subjected only to the forces of respiration because they function rib to rib. Device migration describes the shift of the superior rib cradle proximally into the rib of attachment, or the distal hook migration through the lamina causing dislodgement, or "disattachment." Some of these reported device migrations "through" bone may actually be reactive rib bone growing around the superior cradle giving the appearance of device migration. Some cradles actually erode through the bone and emerge superior to the rib into the surrounding muscle.

There were 13 device fractures in 7 of 33 patients in the feasibility study, but only 6 device fractures in 5 of 214 patients in the multi-center study. When the total number of actual surgical procedures (initial surgeries, expansions and replacements) are considered, the rate of device fractures is 3.3% in the feasibility study (13 events in 398 procedures), and 0.5% in the multi-center study (6 events in 1,140 procedures). There were 50 procedure-related infections in the 1,538 surgical procedures for the feasibility and multi-center studies (3.3%).

During the course of this 14-year study, there were 12 deaths among the 257 patients enrolled in the study, 4 in the feasibility study and 8 in the multi-center study. None of the deaths were determined to be related to the study device by the investigators.

RISK PROBABLE BENEFIT ANALYSIS

TIS is a life threatening condition that affects a small population of children (less than 4000 occurrences per year in the United States). TIS can be seen in any three (3) of the following general diagnostic categories:

- Flail Chest Syndrome
- Rib fusion and scoliosis
- Hypoplastic thorax syndrome

The patient population of this study is a heterogeneous mixture with respect to underlying cause (genetic, congenital, or acquired), severity of symptoms, patient growth, and other medical conditions concurrent with TIS.

Treatment with the VEPTR device has been shown to maintain or improve the AVR in 92.0% of the patients, and the patient survival rate in the VEPTR clinical trial was 95.1%, whereas this condition is frequently terminal with non-surgical treatment. With the VEPTR, allowed growth of the thoracic spine and lungs while controlling severe scoliosis.

Each child with TIS presents a unique combination of factors that dictate the breadth of treatment required. These factors include age, gender, and length of follow-up, diagnosis, overall health and individual growth pattern. Depending on the presenting condition of the patient, any number of risks may be associated with the implantation and maintenance of the VEPTR device. The adverse events experienced in the VEPTR clinical study were presented in Table 6. Consideration also needs to be given to the age of the patient at initial implantation, the numerous other congenital anomalies these patients can have, and their activity levels. In addition, there are numerous factors that predispose these patients to wound infections, and the use of a prophylactic pre-operative and post-operative antibiotic regime and protective bandages at the operative site may decrease the wound infection rate.

The probable benefits associated with patients implanted with the VEPTR device outweigh the risks present for this patient population.