DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date DEC 16 1997

From Deputy Director, Clinical and Review Policy,
Office of Device Evaluation (HFZ-400)
Center for Devices and Radiological Health (CDRH)

Subject Humanitarian Device Exemption Approval of William E. Kaplan, M.D., and Ingrid Richards, R.N., MSN's Urostim - ACTION

To Director, CDRH
Regulations Policy and Management Staff, Office of Policy
(HFZ-26) _____

ISSUE. Publication of a notice announcing approval of the subject Humanitarian Device Exemption (HDE).

FACTS. Tab A contains a FEDERAL REGISTER notice announcing:

(1) an HDE approval order for the above referenced medical device (Tab B); and

(2) the availability of the summary of safety and probable benefit for the device (Tab C).

RECOMMENDATION. I recommend that the notice be signed and published.

Kimber Richter

Kimber Richter, M.D.

Attachments
Tab A - Notice
Tab B - Order
Tab C - Summary of Safety and Probable Benefit(SSPB)

DECISION

Approved ✓ Disapproved ____ Date 12-16-97

Prepared by R.Pagano, CDRH, HFZ-470, 11/25/97, 594-2194

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. _____]

William E. Kaplan, M.D. and Ingrid Richards, R.N., MSN;

Humanitarian Device Exemption Approval of the Urostim

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the humanitarian device exemption (HDE) application by William E. Kaplan and Ingrid Richards, Chicago, IL, under section 520(m) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360j(m)), for the Urostim. FDA's Center for Devices and Radiological Health (CDRH) notified the applicant, by letter on DEC 16 1997, of the approval of the application.

DATES: Petitions for administrative review should be submitted by (insert date 30 days after date of publication in the Federal Register).

ADDRESSES: Written requests for copies of the summary of safety and probable benefit and petitions for administrative review should be submitted to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., Rm. 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Russell P. Pagano,

Office of Device Evaluation,

Center for Devices and Radiological Health (HFZ-470),

Food and Drug Administration,

9200 Corporate Blvd.,

Rockville, MD 20850,

301-594-2194.

SUPPLEMENTARY INFORMATION: On September 12, 1997, William E. Kaplan, M.D. and Ingrid Richards, R.N., MSN, Chicago, IL 60614, submitted an application for an HDE of the Urostim to CDRH. The device is a bladder stimulator and is indicated for use in children for the treatment of neurogenic bladder disease secondary to spina bifida. This HDE was not taken to a FDA advisory panel because similar electrical stimulators for the treatment of incontinence (albeit in different populations with different etiologies) have been in commercial use for over 20 years, i.e., the information in this HDE substantially duplicates information previously reviewed by an advisory panel.

On DEC 16 1997, CDRH approved the application by a letter to the applicant from the Deputy Director, Clinical and Review Policy, Office of Device Evaluation, CDRH.

A summary of the safety and probable benefit upon which CDRH based its approval is on file in the Dockets Management Branch (address above) and is available from that office upon written request. Requests should be identified with the name of the device and the docket number found in brackets in the heading of this document.

Opportunity for Administrative Review

Section 515(d)(3) of the act (21 U.S.C. 360e(d)(3)) authorizes any interested person to petition, under section 515(g)

of the act (21 U.S.C. 360e(g)), for administrative review of CDRH's decision to approve this application. A petitioner may request either a formal hearing under part 12 (21 CFR part 12) of FDA's administrative practices and procedures regulations or a review of the application and CDRH's action by an independent advisory committee of experts under Part 14 (21 CFR Part 14). A petition is to be in the form of a petition for reconsideration under § 10.33(b) (21 CFR 10.33(b)). A petitioner shall identify the form of review requested (hearing or independent advisory committee) and shall submit with the petition supporting data and information showing that there is a genuine and substantial issue of material fact for resolution through administrative review. After reviewing the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the Federal Register. If FDA grants the petition, the notice will state the issue(s) to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

Petitioners may, at any time on or before (insert date 30 days after date of publication in the Federal Register), file with the Dockets Management Branch (address above) two copies each of the petition and supporting data and information, identified with the name of the device and the docket number found in brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under section 520(h) of the act (21 U.S.C. 360j(h)), 21 CFR 814.116(b), and under authority delegated

to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Director, Center for Devices and Radiological Health (21 CFR 5.53).

Dated: DEC 16 1997.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

DEC 16 1997

William E. Kaplan, M.D., and Ingrid Richards, R.N., MSN
Children's Memorial Hospital
2300 Children's Plaza, #24
Chicago, Illinois 60614

Re: H970003
Urostim
Filed: September 12, 1997

Dear Dr. Kaplan and Ms. Richards:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your humanitarian device exemption (HDE) application for the Urostim. This device is indicated for use in children for the treatment of neurogenic bladder disease secondary to spina bifida. We are pleased to inform you that your HDE is approved subject to the enclosed "Conditions of Approval". Please note, however, that as stipulated in section 520(m)(5) of the Federal Food, Drug and Cosmetic Act (the act) (21 U.S.C. 360j(m)(5)), this approval is only valid for a period of 18 months from the date of this approval order. An extension of approval may be requested in accordance with the procedures outlined in the enclosed "Conditions of Approval". Also enclosed in this letter is the Summary of Safety and Probable Benefit for the device, which you have agreed to distribute to all users of the device. You may begin distribution of the device, as discussed below, upon receipt of this letter.

You have informed the FDA that you will not manufacture any new Urostim devices and will only distribute the 30 devices already imported into the United States. Should you want to manufacture the above device for distribution in the United States, you will need to submit a complete description of the manufacturing methods as required under 21 CFR 814.20(b)(4)(v) and you may be subject to an FDA inspection to confirm that the manufacturing facilities, methods and controls are in compliance with the applicable device Good Manufacturing Practice (GMP) requirement, as set forth in the Quality System Regulation (QS) for Medical Devices; General Regulation (21 CFR Part 820). In addition, if you decide to manufacture and market this device, you must submit, as an HDE supplement, copies of all labeling in final printed form.

The sale, distribution, and use of this device are limited to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the act (21 U.S.C. 360j(e)) under the authority of section 515(d)(1)(B)(ii) of the act (21 U.S.C. 360e(d)(1)(B)(ii)). In addition, in order to ensure the safe use of the device, FDA has further restricted the device within the meaning of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act insofar as (1) the labeling shall specify the training requirements for practitioners who may use the device as approved in this order and (2) the sale, distribution, and use must not violate sections 502(q) and (r) of the act (21 U.S.C. 352(q) and (r)).

FDA wishes to remind you that failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act.

CDRH will publish in the **Federal Register** a notice of its decision to approve your HDE. The notice will state that a summary of the safety and probable benefit of the device upon which the approval was based is available to the public upon request. Within 30 days of publication of the notice of approval in the **Federal Register**, any interested person may seek review of this decision

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by requesting an opportunity for administrative review, either through a Part 12 hearing or review by an independent advisory committee, under section 515(g) of the act (21 U.S.C. 360e(g)).

Any information to be submitted to FDA regarding this HDE should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above HDE number to facilitate processing:

Document Mail Center (HFZ-401)
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions concerning this approval order, please contact Russell P. Pagano, Ph.D., at (301) 594-2194.

Sincerely yours,

Kimber Richter

Kimber Richter, M.D.
Deputy Director
Clinical and Review Policy
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures

CONDITIONS OF APPROVAL FOR AN HDE

I. APPROVED LABELING

As soon as possible and before commercial distribution of the device, the holder of an HDE should submit three copies of the approved labeling in final printed form as an amendment to the HDE. The supplement should be submitted to the Document Mail Center (HFZ-401), Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

II. ADVERTISEMENTS

Advertisements and other descriptive printed materials issued by the HDE holder or private label distributor with respect to this device should not recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360j(e)) under the authority of section 515(d)(1)(B)(ii) of the act (21 U.S.C. 360e(d)(1)(B)(ii)), all advertisements and other descriptive printed material issued by the holder or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects, and contraindications.

III. HDE SUPPLEMENTS

Before making any change affecting the safety or probable benefit of the device, the HDE holder should submit a supplement for review and approval by FDA unless a "Special HDE Supplement" is permitted as described under 21 CFR 814.39(d)(2) or an alternate submission is permitted as described under 21 CFR 814.39(e). All HDE supplements or alternate submissions must comply with the applicable requirements under 21 CFR 814.39 of the Premarket Approval (PMA) regulation and under 21 CFR 814.106 of the Humanitarian Device Exemption regulation.

Since all situations which require an HDE supplement cannot be briefly summarized, please consult the HDE regulation for further guidance. The guidance provided below is only for several key instances. In general, an HDE supplement must be submitted:

1) When unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification; or

2) If the device is to be modified, and animal/laboratory or clinical testing is needed to determine if the modified device remains safe and continues to provide probable benefit.

HDE supplements submitted under 21 CFR 814.39(d)(2) "Special HDE Supplement - Changes Being Effected" are limited to the labeling, quality control, and manufacturing process changes as specified under this section of the regulation. This provision allows for the addition of, but not the replacement of previously approved, quality control specifications and test methods. These changes may be implemented upon acknowledgment by FDA that the submission is being processed as a "Special HDE Supplement - Changes Being Effected." Please note that this acknowledgment is in addition to that issued by the Document Mail Center for all HDE supplements submitted. This procedure is not applicable to changes in device design, composition, specifications, circuitry, software, or energy source.

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of an HDE supplement before implementation and include the use of a *30-day HDE supplement* or *periodic postapproval report*. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence to the HDE holder that the alternate submission is permitted for the change. Before this can occur, FDA and the HDE holder must agree upon any needed testing, the testing protocol, the test results, the reporting format, the information to be reported, and the alternate submission to be used.

Please note that unlike the PMA process, a supplement may not be submitted for a new indication for use for a humanitarian use device (HUD). An HDE holder seeking a new indication for use for an HUD approved under the provisions of Subpart H of 21 CFR 814, must obtain a new designation of HUD status for the new indication for use and submit an original HDE application in accordance with §814.104. The application for the new indication for use may incorporate by reference any information or data previously submitted to the agency.

IV. POSTAPPROVAL RECORD KEEPING REQUIREMENTS

An HDE holder is required, for the duration of the period that a HUD is approved for marketing, to maintain records of the names and addresses of the facilities to which the HUD has been shipped, correspondence with reviewing institutional review boards (IRBs), as well as any other information requested by a reviewing IRB or FDA.

V. POSTAPPROVAL REPORTING REQUIREMENTS

Continued approval of the HDE is contingent upon the submission of postapproval reports required under 21 CFR 814.84 and 21 CFR 814.126 and extension requests under 21 CFR 814.120. In order to avoid duplicative reporting, the periodic postapproval reports required under 21 CFR 814.84(b) may be combined with a request for extension. Postapproval reports for supplements approved under the original HDE should be included in the next and subsequent periodic reports for the original HDE unless otherwise specified in the approval order for the HDE supplement.

A. As specified by section 520(m) of the act, an HDE is valid for a term of 18 months from the date of approval but can be extended at 18-month intervals. In order to avoid the risk of a lapse in marketing approval, the holder of an HDE wishing to obtain an extension should submit such a request to FDA at least 90 days prior to the expiration of the HDE. Three copies of the request for extension, with the outside envelope plainly marked "Request for Extension of HDE Approval", should be submitted to the Document Mail Center (HFZ-401), Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The submission should state the applicant's name and address, the HDE number, and should include the following information based upon the first 12 months of experience with the device following the most recent HDE approval or extension:

(1) An update of the information required under §814.102(a) in a separately bound volume;

(2) An update of the information required under §§814.104(c)(2), (c)(3), and (c)(5);

(3) The number of devices that have been shipped or sold and, if the number shipped or sold exceeds 4,000, an explanation and estimate of the number of devices used per patient. If a single device is used on multiple patients, the applicant shall submit an estimate of the number of patients treated or diagnosed using the device together with an explanation of the basis for the estimate;

(4) Information describing the applicant's clinical experience with the device. This shall include safety information that is known or reasonably should be known to the applicant, a summary of medical device reports made pursuant to 21 CFR 803, any data generated from postmarketing studies, and information (whether published or unpublished) that is known or reasonably expected to be known by the applicant that may affect an evaluation of the safety of the device or that may affect the statement of contraindications, warnings, precautions, and adverse reactions in the device labeling; and

(5) A summary of any changes made to the device in accordance with supplements submitted under §§814.108 and 814.39(b).

B. If the HDE holder does not wish to maintain marketing approval for the humanitarian use device and thus does not submit an extension request, a final report should be submitted no later than 90 days following the expiration of the period of marketing approval. Three copies, identified as "Final Report" and bearing the applicable HDE reference number, should be submitted to the Document Mail Center at the address provided above. The final report should include the following information required by 21 CFR 814.126(b)(1):

(1) An estimate of the number of patients who were treated or diagnosed with the device and the number of devices shipped or sold since initial marketing approval under the humanitarian device exemption. (If the number of devices shipped or sold exceeds 4,000 per year, an explanation and estimate of the number of devices used per patient shall be included. Similarly, if a single device is used on multiple patients, the applicant shall submit an estimate of the number of

patients treated or diagnosed using the device together with an explanation of the basis for the estimate.);

(2) Information regarding the retrieval or disabling of unused devices, a summary of results and conclusions with regard to the clinical use of the device, and a summary of the medical device reports submitted under 21 CFR 803; and

(3) A summary and bibliography of published and unpublished data, reports, and studies involving the device that are known to or that reasonably should be known to the applicant and were not previously submitted to FDA. If, after reviewing the summary and bibliography, FDA concludes that a copy of the unpublished or published information is needed, FDA will notify the holder that copies shall be submitted.

C. **ADVERSE REACTION AND DEVICE DEFECT REPORTING**

As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and probable benefit of the device, the holder shall submit three copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the Document Mail Center (HFZ-401), Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. Such reports should be submitted within 10 days after the HDE holder receives or has knowledge of information concerning:

(1) A mixup of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved HDE that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the HDE holder's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the firm. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the holder shall be included in the "Request for Extension of HDE Approval" described under "Postapproval Reports" above unless otherwise specified in the conditions of approval for this HDE. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of occurrence for each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the HDE holder when determined by FDA to be necessary to provide continued reasonable assurance of the safety and probable benefit of the device for its intended use.

D. REPORTING UNDER THE MEDICAL DEVICE REPORTING REGULATION

The Medical Device Reporting regulation (MDR) (21 CFR 803) became effective on April 11, 1996 and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to FDA whenever they receive or otherwise became aware of information that reasonably suggests that one of its marketed devices:

(1) may have caused or contributed to a death or serious injury; or

(2) has malfunctioned and that the device or any other device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Events subject to reporting under the MDR regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements. FDA has determined, however, that such duplicative reporting is unnecessary. Therefore, whenever an event involving a device is subject to reporting under both the MDR regulation and the "Adverse Reaction and Device Defect Reporting" requirements, the report should be submitted in compliance with Part 803 and identified with the HDE reference number to the Division of Surveillance Systems (HFZ-531), Center for Devices and Radiological Health, Food and Drug Administration, 1350 Piccard Drive, Rockville, Maryland 20850. For questions regarding the MDR regulation, please call (301) 594-2735.

Events included in periodic reports to the HDE that have also been reported under the MDR regulation must be so identified in the periodic report to the HDE to prevent duplicative entry into FDA information systems.

Copies of the MDR regulation and an FDA publication entitled, "An Overview of the Medical Device Reporting Regulation," are available by written request to the address below or by telephoning 1-800-638-2041.

Division of Small Manufacturers Assistance (HFZ-220)
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Lane
Rockville, Maryland 20850

SUMMARY OF SAFETY AND PROBABLE BENEFIT

I. GENERAL INFORMATION

Device Generic Name: Bladder Stimulator

Device Trade Name: Urostim Bladder Stimulator

Applicant's Name and Address:

William E. Kaplan, M.D. and Ingrid Richards, R.N., MSN
Children's Memorial Hospital
2300 Children's Plaza, #24
Chicago, Illinois 60614

Humanitarian Device Exemption (HDE) Number: H970003

Date of Humanitarian Use Device Designation: September 2, 1997

Date of Panel Recommendation: The HDE was not taken to Panel. Please see Section X of this document for the rationale used in determining that panel review was unnecessary.

Date of Good Manufacturing Practice Inspection: The Good Manufacturing Practice (GMP) inspection requirement for this HDE was waived because the sponsor has no intent to manufacture or market any new devices. The HDE is only being approved for those devices that were distributed for use in the clinical study and, through this use, have been shown to function as intended. In addition, the manufacturing procedure used in making the devices was certified by the Austrian Association for Certificates and Quality Safety Control as being a Quality Management System that meets the ISO 9001:1994 norm.

Date of Notice of Approval to the Applicant: DEC 16 1997

II. INDICATIONS FOR USE

The device is indicated for use in children for the treatment of neurogenic bladder disease secondary to spina bifida.

III. DEVICE DESCRIPTION

The Urostim consists of a single channel stimulator and an electrode/catheter. The stimulator generates a monophasic pulse. The device has an available output voltage of ± 25 volts and an output current of ± 10 milliamps with an output pulse width of 6 milliseconds at 60-70 Hz. The device is preprogrammed with 12 treatment regimens. The device output can range from 0 - 10 mA. The physician increases the amperage (in increments of 0.1 mA) until the desired bladder response has been elicited.

The stimulator has the following buttons/features:

1. An On/Off button that turns the device on or off. In the off mode, the device will store the previously displayed parameters. When the device is turned on, the current setting automatically resets to zero.

2. Amplitude buttons are used to increase or decrease the current in 0.1 mA increments. The current automatically goes to zero when the device is turned on, a new regimen is selected, or the timer runs to zero (treatment ends).

3. A Start/Stop button begins or interrupts the stimulation treatment. The stimulation will also end when the timer reaches zero.

4. Up/Down buttons are used to change the program regimen. A program select button will illuminate (red LED) for six seconds and the main display (#5 below) will illuminate the chosen program number. Once one of the aforementioned 12 programs is selected, the device automatically loads the stored parameters.

5. An 8-character LCD display shows the current (mA) being applied unless another panel button is used (e.g., If the program is changed, the LCD will illuminate the program number for six seconds. During this time, the light on the program select button will also be lit.)

6. A low battery LED will light if the battery voltage goes too low. The stimulator is powered by a standard 9.5 volt alkaline battery. The device will automatically shut-off if the battery voltage drops below 6.5 volts.

This stimulator weighs 6 ounces and measures 2.65" (W) x 4.3" (L) x 0.9" (H).

The electrode/catheter consists of a catheter with the conducting electrode at the distal end. The electrode is completely enclosed in the catheter material (polyvinyl chloride (PVC)).

A return electrode (not included) is also needed to operate the device.

The device has the following safety features: 1) designed to meet UL 544, 2) the Stop button immediately discontinues all stimulus output, and 3) a panel covers the controls to help prevent inadvertent contact by the user.

Software in the device controls various safety functions such as: 1) resetting the amplitude to zero prior to each treatment, 2) emitting an audible alarm if either electrode becomes disconnected, and 3) shutting off the device when the battery voltage drops below 6.5 volts. The software is hardcoded and cannot be modified by the user.

IV. CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

Contraindication: The device is contraindicated in any patient with a demand type pacemaker or any patient with known or suspected heart disease.

Contraindication: The device is contraindicated in any patient with a completely denervated bladder.

Precaution: The long-term effects of chronic electrical stimulation are unknown.

Precaution: Additional care should be taken if treating a patient with known or suspected epilepsy.

Precaution: Additional care should be taken if treating a female during menstruation.

Precaution: This device should only be used under the care of a physician thoroughly trained by the sponsor.

V. ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The following adverse events have been reported in either the clinical study or in the medical literature:

1. Urinary tract infections (UTIs);
2. Pain in the urethra or bladder;
3. Bladder infections; and
4. Skin irritation/burn at the grounding site.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Many of the children with neurogenic bladder disease secondary to spina bifida can manage their condition with drugs or clean intermittent self-catheterization. Of these children, approximately 17% have unacceptable urodynamic patterns (e.g., dangerously high bladder pressures and/or unacceptable outlet resistance)[1] . These patients require immediate medical attention which often consists of clean intermittent catheterization for older children, drug therapy for newborns, and/or a diversionary surgical procedure relatively early in life. The other ~83% of patients have a better urodynamic profile, however, these patients also can have significant urinary incontinence problems. In some of these cases, augmentation surgery may be required to increase the patient's bladder capacity. This is a major surgical procedure which typically consists of attaching a piece of bowel to the bladder to increase the bladder size. In addition to events associated with all abdominal surgery, bladder augmentation can also result in the following adverse events:

- increase in the occurrence of UTIs;
- a greater propensity to forming bladder stones;
- formation of a fistula;
- surgical revision due to leakage around or breakage of the pouch seal;
- excess mucus production which may plug catheters;
- urinary incontinence;
- ureteral reflux;
- GI tract disorders;
- GU tract bleeding

- pulmonary disorders;
- venous thrombosis;
- bowel neoplasia;
- hypokalemia;
- hypercloremia; and
- high post-void residual.

All of the current practices for managing/treating children with neurogenic bladder disease secondary to spina bifida have significant deficiencies. None of the three main treatments of choice (drug therapy, intermittent catheterization, or surgery) cure the majority of patients with this disease. In fact, drug therapy and self-catheterization are long-term management tools and do not treat the patient's condition. In addition to being a long-term management tool, the effectiveness of drug therapy can also vary and lessen with time. Intermittent catheterization can alleviate the problem indefinitely for some patients, however, this management tool presents social limitations as well as medical risks (e.g., increased risk of infection) to the child. While the increased bladder volume achieved from surgery may lessen or reduce the urinary difficulties of some patients, in many cases it does not eliminate the need for long-term intermittent catheterization. The intermittent catheterization is still needed because augmentation surgery does not increase a child's ability to feel sensations in the bladder. This ability is needed for a child to achieve a therapy-free acceptable voiding pattern.

It should be noted that use of the Urostim device will not preclude a patient from choosing an alternative approach to his/her problem. In addition, the daily sessions ensure that the patient's condition is being monitored by a qualified physician while the bladder stimulation option is being tried.

VII. MARKETING HISTORY

This type of bladder stimulator has been marketed in Europe for more than 10 years, and there are no reported instances where the device was removed from the market for any safety or effectiveness concern.

VIII. SUMMARY OF STUDIES

A. Preclinical Studies

Limited preclinical information is presented in the HDE, however, this information provides some assurance that the device is biocompatible and does not present serious electromagnetic compatibility concerns. Because of the limited nature of these data, the safety of the device has been based on the clinical use described below.

B. Clinical Study

In 1991, FDA informed Dr. Kaplan that the agency considered any studies involving this device to be Non-Significant Risk (NSR) and could be conducted without an FDA-approved Investigational Device Exemptions (IDE) application.

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The HDE contains a report on a clinical trial of 597 patients upon whom the device has been used. Because of the nature of the trial, the data on these patients cannot be used to definitively show effectiveness of the device for the proposed indication. However, since the patient population consists primarily of children who were treated with the device in the same fashion as those with the proposed indication, these data are applicable in determining the safety profile of the device. Based on thousands of procedures on hundreds of patients, there is no evidence that any serious adverse event will occur if this device is used as indicated.

The clinical trial data do show that the device may provide a probable benefit to the proposed patient population. This probable benefit includes an increased rate of growth of, and/or an increased level of sensation in, the child's bladder. Either of these changes may provide a clinical improvement in a patient's urinary outflow disorder.

Children with neurogenic bladder disease secondary to spina bifida experience bladder growth at a much slower rate (typically 20 to 25% less growth) than age-matched neurologically intact children. The most compelling aspect of Dr. Kaplan's research is that, with the use of the stimulation regimen, 53% of patients experienced an increase in bladder capacity of > 20%[3]. This increase presents a two to three-fold increase over the bladder capacity of untreated patients[2,3]. These results also compare favorably to growth seen in children without this disorder. The benefits of increased bladder capacity (while maintaining or reducing the patient's intravesical storage pressure)[2] include lessening the need for bladder augmentation surgery and improvement of symptoms of urinary incontinence.

Another important reported benefit of the device is the improvement of bladder sensation which is very helpful if a child is to ever achieve continence. While the data showing improved sensation are not conclusive, they do provide additional support to the probable benefit of this treatment.

The clinical trial further indicates that appropriately trained physicians have a better chance of providing a patient the above probable benefits. This statement is also supported by Dr. Kaplan[2]. Based on this fact, Dr. Kaplan has agreed to train all clinical staff that will use the device and also to act as a consultant to the staff until sufficient experience has been obtained at a given site.

IX. CONCLUSIONS DRAWN FROM THE STUDY

The results from the clinical study and published literature provide adequate assurance that the devices used in the trial do not present an unreasonable risk of illness or injury to the patient. The limited clinical data suggest that the device could provide benefit to children with neurogenic bladder disease secondary to spina bifida. The lack of preclinical and manufacturing information, however, precludes the agency from approving any devices other than those distributed for use in the clinical study. A total of 30 devices to 16 sites were distributed by Dr. Kaplan and Ms. Richards.

In conclusion, the clinical data show that the risk of injury or illness to the patient from this device is very low and these data further suggest probable benefit to health from the use of the device. Taking into account the risks and benefits of currently available

devices or alternative forms of treatment, it is believed that the probable benefit of this device outweighs the risk.

X. PANEL RECOMMENDATIONS

This HDE was not taken to an Advisory Panel because other electrical stimulators for incontinence, albeit of different etiologies in different patient populations, have been in use in the United States for over 20 years. Therefore, the information in this HDE substantially duplicates information previously reviewed by this panel.

XI. CDRH DECISION

CDRH determined that, based on the data submitted in the HDE, the Urostim Bladder Stimulator will not expose patients to an unreasonable or significant risk of illness or injury, and the probable benefit to health from using the device outweighs the risk of illness or injury, and issued an approval order on DEC 16 1997

XII. APPROVAL SPECIFICATIONS

Directions for Use: See the Physician Labeling and Patient/Guardian Information
Hazards to Health from Use of the Device: See indications, contraindications, warnings, precautions, and adverse effects in Sections IV and V (above).

XIII. REFERENCES

1. Kaplan, William E., "Alternative to Enterocystoplasty II, Bladder Stimulation," Problems in Urology, Vol. 8, No. 3, 1994, pp. 410-415.
2. Cheng, Earl Y., et.al. (including William Kaplan and Ingrid Richards), "Bladder Stimulation Therapy Improves Bladder Compliance: Results From a Multi-Institutional Trial," J. Urol., Vol. 156, 1996, pp. 761-764.
3. Palmer, Lane S., I. Richards, and W. E. Kaplan, "Age-Related Bladder Capacity and Bladder Capacity Growth in Children with Myelomeningocele," Presentation at the American Academy of Pediatrics, Section on Urology, Boston, October 1996.

PHYSICIAN LABELING

UROSTIM BLADDER STIMULATOR

Contact Information:

William E. Kaplan, M.D. and Ms. Ingrid Richards, R.N., MSN
2300 Children's Plaza, Box 24
Chicago, Illinois 60614
(773) 880-4428 or (773) 880-4381

Indications for Use:

The Urostim is intended to be used in children to treat neurogenic bladder disease secondary to spina bifida.

Contraindications, Warnings, and Precautions:

See the Summary of Safety and Probable Benefit (SSPB).

Instructions for use:

Prior to treating a patient with this device, the user should thoroughly review the SSPB and Operating Manual (supplied by the above contacts) and have received training in patient selection and device use from the above contacts.

Patient/Guardian Information
Urostim Bladder Stimulation Program

What is the Urostim Bladder Stimulator?

The Urostim is a medical device that may help some children with problems with their bladder/urination when these problems were caused by Spina Bifida. Your child has been identified by his/her doctor as possibly being able to benefit from treatment with the Urostim. While the advantages of this treatment have not been conclusively demonstrated, it is believed that bladder stimulation will provide your child with a probable benefit to his/her bladder condition. The Urostim may help your child to:

- Increase his/her bladder capacity. Your child may be able to store urine more easily which, in turn, may help reduce incontinence (the lack of ability to hold urine).

- Start or increase feelings in his/her bladder. This may let your child "feel" when the bladder is full. This will tell him/her when to use the bathroom or to use a catheter (a tube to drain urine from the bladder).

- Give him/her effective bladder contractions. This may let your child control his/her urine flow better.

What makes up the Urostim?

The Urostim is a hand-held device that has two main components. The "control box" looks like a television remote control and contains buttons that allow the doctor to program the settings that he/she believes will provide your child with the most benefit. Attached to this box is the Urostim catheter that contains electrodes through which the box sends electricity. This catheter is placed in your child's bladder through his/her urethra (the opening through which urine passes out of your body when you urinate) and a small (and safe) amount of electricity is applied to your child's bladder. This electricity is the "stimulation" that will hopefully provide your child with some of the benefits described above.

What is the treatment program and how much time will it take?

- *What is the Treatment Program?* The treatment program consists of daily outpatient therapy that will last approximately three to four weeks per series. Your child will have a catheter placed through his/her urethra and into the bladder (your nurse can provide you with pictures that show you where your urethra and bladder are located). Sterile water will be placed into your child's bladder through the Urostim catheter. A small amount of electrical current travels through the device and the walls of your child's bladder will be stimulated.

- *How Much Time is Involved?* Each treatment will last approximately 90 minutes. The treatments are repeated every day for three to four weeks. After these three or four weeks, your child will not receive treatment for three to six months. After the three to six months, your child's condition will be checked by your doctor and it may be recommended that another treatment program of one to two weeks be given to your child. You should be aware that having your child treated by this device will take a lot of time and effort on your part and that there are no guarantees that successful results will be achieved.

- *Will my Child be in Pain?* Although it is possible that your child may feel something in his/her bladder while being treated, most children will not experience pain from the electrical current.

- *Is the Electricity Dangerous to my Child?* No, the amount of current supplied is very low and should not present any electrical risk to your child.

- *Will my Child be Awake for the Treatment?* Yes, your child will be awake and laying on a doctor's table. You may be with your child during the treatment.

Why might this device work on my child?

- *His/her nerves may not be working right.* It is believed that stimulating the walls of your child's bladder will help "wake-up" nerves in the bladder that are currently not functioning properly. For this reason, only children (like yours) with at least a partially intact spinal cord may benefit from the procedure. Children with your child's condition often have the nerve pathways interrupted and the nerves are not sending the right messages between the bladder and the brain. Good communication between the bladder and brain is what allows people to recognize bladder fullness which is an essential part of learning when you need to use the bathroom.

- *His/her bladder may not be growing at a normal rate.* One additional side effect of your child's condition is that his/her bladder will not grow as quickly or as large as typically seen in children of the same age. This slow-growing, small bladder can cause additional serious health concerns as your child ages. Because there is some evidence that the stimulation procedure may help your child's bladder grow at near normal rates, it is believed that the procedure could possibly prevent future serious health conditions.

What are the risks of this procedure?

There have been hundreds of children treated with this procedure and very few adverse events have been recorded. However, it is possible that the following could occur:

- Pain/irritation in the urethra or bladder.

- A bladder infection.

- An electrical burn at the grounding site.

Additional Questions

If you have any additional questions, you should contact one of the following people prior to beginning this program.

Ms. Ingrid Richards, R.N., MSN
2300 Children's Plaza, Box 24
Chicago, Illinois 60614
(773) 880-4381
or Dr. William E. Kaplan
(773) 880-4428