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SUMMARY MINUTES

OF THE

GASTROENTEROLOGY AND UROLOGY DEVICES

ADVISORY PANEL MEETING

OPEN SESSION

October 19, 2000

**Best Western Washington Gateway Hotel
Grand Ballroom
1251 West Montgomery Avenue
Rockville, Maryland**

**Gastroenterology and Urology Devices
Advisory Panel**

October 19, 2000

Panel Participants

Anthony N. Kalloo, M.D.
Panel Chair
Gastroenterologist
The Johns Hopkins University

Craig F. Donatucci, M.D.
Voting Member
Urologist
Duke University Medical Center

Joseph H. Steinbach, Ph.D.
Voting Member
Biomathematician
V.A. Medical Center

Diane K. Newman, RNC
Consumer Representative
DKN Medical Associates

Michael S. Banik
Industry Representative
Boston Scientific

Robert R. DiLoreto, M.D.
Temporary Voting Member
Urologist
Michigan Institute of Urology

Richard Gorman, M.D.
Temporary Voting Member
Pediatrician
Private Practice

Martin Kaefer, M.D.
Temporary Voting Member
Pediatric Urologist
Indiana University/Riley Children's Hospital

Naida B. Kalloo, M.D.
Temporary Voting Member
Pediatric Urologist

FDA Participants

Jeffrey W. Cooper, D.V.M.
Executive Secretary, Gastroenterology and Urology Devices Panel

Daniel Schultz, M.D.
Acting Director
Division of Reproductive, Abdominal, and Radiological Devices

Elisa Harvey, D.V.M., Ph.D.
Acting Chief
Urology and Lithotripsy Devices Branch

Dave Segerson
Associate Director
Division of Reproductive, Abdominal, and Radiological Devices

John Baxley
Biomedical Engineer

Hector Herrera, M.D., M.P.H.
Medical Officer and Urologist

Judy Chen
Statistician

Sponsor Participants

Dr. Claes Mörlin (Q-Med)
Dr. Göran Läckgren (Clinical Investigator)
Dr. Nicola Capozza (Clinical Investigator)
Dr. Bengt Agerup (Q-Med)
Dr. Hege Bothner Wik (Q-Med)
Mark Yacura (Buchanan Ingersoll)
Ted Sullivan (Buchanan Ingersoll)

OPEN SESSION

Panel Chair Anthony N. Kalloo, M.D., called the session to order at 9:31 a.m., noting that the voting members present constituted a quorum and asking the panel members to introduce themselves and give their areas of expertise.

Panel Executive Secretary Jeffrey W. Cooper, D.V.M., read appointments to temporary voting status for Drs. Gorman, Kaefer, and Naida Kalloo, noting that Dr. Gorman was a consultant to the Center for Drug Evaluation and Research. Dr. Cooper also read the conflict of interest statement, noting that Ms. Diane Newman had declared a past interest in the sponsoring firm on an unrelated issue and her full participation was permitted. He listed tentative future panel meeting dates as March 9, June 29, September 13, and December 7, 2001.

OPEN PUBLIC HEARING

There were no requests to address the panel from the audience.

OPEN COMMITTEE DISCUSSION--PREMARKET APPROVAL

APPLICATION P00029 FOR Q-MED'S DEFLUX INJECTABLE GEL

Sponsor Presentation

Dr. Claes Mörlin introduced the sponsor team. **Dr. Bengt Agerup** explained the composition of the Deflux device, which is an injectable gel composed of dextranomer particles and a hyaluronic acid carrier. Dr. Agerup listed the uses of dextran in various fields, in particular as a plasma volume expander, and the mechanism of action, with special focus on particle size and its relationship to the possibility of particle migration.

Dr. Hege Bothner Wik explained the conclusions drawn from preclinical data. Animal studies showed no adverse reactions, and the injected material remained stable.

Histopathologic observations showed that the Deflux reflected a good tissue tolerance with an expected foreign body reaction at injection site and no significant side effects. Studies showed no translocation of implant material to other tissues within two years, no cytotoxicity, no delayed contact hypersensitivity in guinea pigs, and no mutagenicity. It produced acceptable induced reactions after implantation in rabbit muscle and intracutaneously. Hemolysis was less than 5 %, and no change in DNA profile was observed in animal studies.

Dr. Göran Läckgren listed treatment options for vesicoureteral reflux (VUR), which include prophylactic antibiotics, surgery, and endoscopic injection of bulking agents, which is not approved in the United States for grades I-III VUR. He listed the advantages of endoscopic treatment, noting that it provides a cost-effective alternative to antibiotic prophylaxis that can be done as an outpatient procedure. He reviewed technical aspects of the Deflux injection and showed a video of the procedure.

Dr. Läckgren also reviewed the Deflux 1 study, a nonrandomized safety and efficacy study in Sweden of 50 children older than one year of age with VUR grades III-IV. He listed inclusion and exclusion criteria and explained the study design and demographic profile. Safety data results included adverse event rates, clinical laboratory findings, ultrasound findings, and rates of urinary tract infections (UTIs), none of which raised serious safety concerns. Using the protocol definitions, efficacy results at 12 months showed a 64% success rate (no reflux), an 11% positive rate (improvement), and a 25% failure rate per ureter.

Dr. Nicola Capozza presented data from the Deflux II nonrandomized study in Italy of 120 children with VUR grades II-IV. He outlined study objectives, inclusion and

exclusion criteria, study design, and demographic characteristics. Dr. Capozza discussed safety in terms of adverse events, clinical laboratory findings, glomerular filtration, and ultrasound findings, none of which raised concerns. Efficacy results at 12 months post-treatment, according to protocol definitions and analyzed per ureter, showed a success rate of 68%, a positive rate (improvement to grade I) of 8%, and a failure rate of 24%.

Dr. Capozza presented data from the Deflux III study, which was a randomized study in Italy comparing the Deflux implant to long-term prophylactic treatment with antibiotics by means of micturition urethro cystography or MUCG results at one-year post-treatment. He explained the study design, inclusion and exclusion criteria, and demographics, noting that there were 99 patients screened, with 38 not included. Of the remaining 61, 21 received long-term prophylaxis and 40 received the implant, with 31 of the latter finishing the protocol. Safety results showed one adverse event and nine episodes of UTI during the study period. Efficacy results showed a cure rate of 69% of Deflux patients with VUR grade greater than or equal to II, compared to a cure rate of 33% of those on antibiotic prophylaxis.

Questions to the sponsors from the panel members included clarification of the protocol, length of follow-up, expected length of treatment effect, animal study data on displacement and longevity of the implant, histopathologic studies, and possible differentiation of retreatment rates by grade of pretreatment VUR. Several panel members had questions regarding the procedures for blinded reading of ultrasounds, the learning curve for physicians injecting the gel, and the recommended use of prophylactic antibiotics during treatment.

FDA Presentation

John Baxley, biomedical engineer in the Urology and Lithotripsy Devices

Branch, introduced the FDA presentation and the FDA review team. He noted that the PMA was granted expedited review because the device met regulatory criteria of treating an irreversibly debilitating condition and having the potential to offer a clear, clinically meaningful advantage over alternatives.

Mr. Baxley described the device and its intended use and the mechanism of action, which increases tissue bulk to produce coaptation of the ureteral orifice and thus blockage of refluxing urine. Chemical testing verified sufficiently low levels of impurities; and biocompatibility testing for cytotoxicity, hemolysis, sensitization, intracutaneous toxicity, and mutagenicity produced no concerns. Biocompatibility testing included 90-day muscle implantation in rabbits, two-year bladder submucosa implantation in rabbits and dogs, and a migration study in rabbits. The tests showed that particle migration was unlikely and carcinogenicity and reproductive toxicity testing was not warranted. Other preclinical tests on injectability time and peak force, as well as stability, produced satisfactory results.

Mr. Baxley noted that the clinical studies were performed in Uppsala, Sweden, and Rome, Italy, and he summarized the conditions under which the FDA accepts foreign data. Studies 1 and 2 were done with no control population and were designed as safety studies only. Renal damage was not thoroughly assessed, and there were some missing data. Study 3 was a randomized, controlled trial designed to assess safety and effectiveness that assessed renal damage and followed patients closely. General FDA concerns with Study 3 involved the fact that it was a single site study; there were also

questions on whether patient demographics and baseline characteristics were sufficiently diverse and whether the range of treatment methods was sufficient. In addition, the FDA raised the possibility of investigator bias, given that the evaluation of reflux grades was not blinded.

Hector H. Herrera, M.D., M.P.H., medical officer and urologist in the Urology and Lithotripsy Devices Branch, gave the FDA clinical review, noting that this was the first bulking agent to request clearance for this intended use. He explained the international classification system for grading reflux and also the mechanism of action and injection method for Deflux. Success for the device studies was defined as no reflux at 12 months; failure as persistent reflux.

Dr. Herrera described patient randomization in Study 3, the primary study. This single-center study randomized 61 patients into a control arm of 21 patients treated with antibiotics only and an implant arm of 39 patients treated with Deflux. Both arms were highly similar at baseline; the majority of all patients were Caucasian. Dr. Herrera summarized that effectiveness results at 12 months showed a 33% patient success rate for control and a 69% patient success rate for Deflux in Study 3.

Dr. Herrera also gave overviews of Study 1 in Sweden, which showed a 56% patient success rate in 43 patients and of Study 2 in Italy, which showed a 61% patient success rate in 107 patients. Retreatment consisted of a single reinjection offered to Deflux patients with persisting reflux at three months, with retreatment rates varying from 16% to 27% in the studies. Baseline grade of VUR appeared to have a strong impact upon the success of Deflux treatment, ranging from 90% effectiveness for Grade II to 33% for Grade IV in Study 3.

Dr. Herrera outlined safety measures in Study 3, which consisted of scintigraphy, serum chemistries, ultrasound, and IVP for kidney and bladder function and kidney/ureter status (no deterioration in either arm), UTIs (9 in Deflux arm, 0 in control), and reporting of adverse events (0 in Deflux arm, 1 in control). In Studies 1 and 2, scintigraphy, serum chemistries, and IVP either were not assessed post-treatment or were predominantly missing. These studies found no increase in ureteral dilatation either study. Study 1 reported no UTIs but two cases of nausea, vomiting and pain post-injection. Study 2 reported 8 UTIs but no adverse events.

Dr. Herrera concluded that Deflux appeared to offer clinically significant improvement, but that the impact of a non-blinded evaluator and a single site study should be assessed. He thought that the safety profile was good, but several statistical issues should be addressed, as would be noted in the statistical review. Dr. Herrera noted that long-term safety of more than two years was unknown but was not, in his opinion, as critical in this entity as in others.

Judy Chen, statistician, gave the statistical review. Her primary concern with the Deflux 1 and 2 studies was whether the observed improvement was due to the device, spontaneous improvement over time, regression to the mean, or all of the above. She also noted the statistical concern that ureter-based success rates would have a larger variance because outcomes of within-patient ureters are likely to be correlated. In the randomized control study, protocol deviations included the fact that two centers were specified but only one entered patients, endpoint evaluation was not masked in the study, and control antibiotic treatment compliance was poor. She also commented that since ureters in the same patient are likely to be correlated, the statistically highly significant treatment

difference is not reliable. No covariable adjustment was done in the sponsor's per-ureter analysis or per-patient analysis. Ms. Chen concluded that given these deficiencies, the data should be reanalyzed by the sponsor and the FDA to validate the sponsor's statistical conclusion, and that the results should be interpreted with the other deficiencies in mind.

Dr. Daniel Schultz, acting director of the Division of Reproductive, Abdominal, and Radiological Devices, joined the session at this point and presented plaques of appreciation to outgoing panel member Craig Donatucci, M.D., and former panel executive secretary Mary Jo Cornelius.

Primary Panel Review

Dr. Naida Kalloo, reviewer for the panel, stressed that it is infection, not reflux, that causes damage, and that the sponsors had demonstrated a success rate for preventing reflux but not infection. She suggested that the panel discuss the role of antibiotics with and without the procedure, saying that stopping antibiotics post-treatment does not necessarily achieve the goal of preventing infection. Dr. Kalloo urged that patients must have antibiotic coverage throughout the 12-month post-treatment period and until the physician can prove that reflux is gone. She speculated about long-term patient management, given the lack of long-term data on success and failure rates, and noted that the long-term effects on the body are unknown. Dr. Kalloo also saw a problem in basing approval for the device on a study of 61 patients and had issues with data collection and insufficient follow-up, which prompted her to ask whether there was enough information to be reanalyzed.

Ms. Chen of the FDA replied that statistical reanalysis could be done on the effect of covariables such as age and disease grade on per patient success in Study 3. Gender, race, and the effect of retreatment should also be analyzed.

Panel Discussion of FDA Questions

1) Should the intended use statement specifically limit the use of Deflux Injectable Gel to patients with particular grades of VUR?

The majority of the panel agreed that Deflux was a viable treatment option, based on its demonstrated success rate, for those not wanting antibiotic treatment for a long period and for those wishing to avoid major surgery. Treatment of grade IV VUR should not be excluded in the labeling indications, but parents should be informed that the success rate for this grade is less than 50% and informed consent should be mandatory. Physicians should also ensure that this treatment is not used alone but that antibiotic coverage and/or other means are used to monitor and treat urinary infection and prevent renal damage. Certain limitations such as not using the procedure with patients with a dysfunctional kidney or with patients with inappropriate voiding problems should also be noted.

2) Are the results from Study 3 sufficient to assess device safety and effectiveness, given possible differences between the demographics and baseline characteristics of the study and the intended U.S. patient population and the possible differences in device use across physicians?

The panel agreed that the study demographics were adequate although narrow and did not pose a major issue, particularly as reflux is more a problem in the population studied than in the general population. Larger panel concerns were the single-site nature of the study,

the small number of patients studied, and the unblinded patient evaluation. There were concerns over patient compliance in the antibiotic control arm and whether the control data were therefore sufficient. Several members thought the data insufficient to establish efficacy and underscored the lack of long-term data. They urged that more information should be provided and stratified by age, gender, degree of reflux, and results.

The panel thought the differences among physicians on device use probably did not warrant concern and that the learning curve for the device would be relatively short, but it was noted that there were not enough sites or physicians studied to be definitive.

3) Does the panel believe that the potential for investigator bias significantly impacts the conclusions of Study 3 regarding effectiveness?

The panel thought the potential for bias did not have a major impact on post-treatment analysis, but were more concerned about pre-treatment bias. They suggested a review committee for pretreatment assessment of VUR grade or a pre and post-treatment assessment and stratification of results done by committee.

4) Does the panel believe that Deflux has a favorable risk/benefit ratio?

The panel agreed that the risk/benefit ratio was favorable overall but thought that lack of long-term data made evaluation difficult. Long-term concerns include migration and the slow failure rate.

5) Is postapproval study/surveillance needed to address any unresolved safety and effectiveness issues?

After considerable discussion, the panel agreed that if Deflux is approved, then there should be more premarketing information collected and analyzed from the patients who were in the study at two years on long-term side effects and on antibiotic use.

Postmarket surveillance should be conducted to look at already treated patients and collect follow-up results through VCUGs at three, 12, and 24 months, ultrasound, and surveillance urinary cultures. A multicenter, multi-investigator postapproval study would be desirable to obtain more safety data on issues such as effect of Deflux on nephritis, transplant, and bladder cancer. If the device is not approved, more information on those in this study should be included to make it approvable and thought should be given to designing a U.S. study to address the incidence of UTI, nephritis, and bladder pathology after Deflux use.

6) Should physician training be required prior to use of Deflux?

The panel consensus was that physician training should not be mandatory, but physicians should be well versed in treatment of reflux, and a training video as well as hands-on training should be made available to physicians who desire it.

7) Are the proposed "Directions for Use" accurate and comprehensive?

The panel recommended that labeling and handouts be completely revised, with specific inclusion and exclusion criteria from the study included in the labeling, such as exclusions or contraindications for patients with a Hutch diverticulum and dysfunctional voiding or multiple ureters. The comment about the length of time that biodegradable material will remain in place should be struck, and the data presented to the panel should be used for the one-year human follow-up data. Statements such as the rate of clinical cure should be struck unless they reflect such data. More information on age groups, sexes, and reflux grades studied should be included, as should rates of spontaneous remission. Patient counseling information should be rewritten to include other therapeutic options.

OPEN PUBLIC HEARING

There were no requests to address the panel.

FDA CLOSING COMMENTS

There were no remarks from FDA representatives.

SPONSOR CLOSING COMMENTS

Sponsor representatives clarified procedures in the Swedish study, including the fact that antibiotic prophylaxis was given until the reflux was gone and that patients who failed to comply with protocols regarding diary notes on antibiotic use in the other studies may still have complied with the protocol. Sponsors thought that it would be possible to get follow-up data on Study 3 and probably on Study 2.

PANEL VOTE

Dr. Cooper read the panel voting instructions and options and thanked **Dr. Naida Kalloo** for her review.

A motion was made and seconded to recommend the PMA as approvable with the following general conditions:

- 1) revised labeling
- 2) a mandatory post-market study
- 3) collection of additional long-term data from existing studies

Vote on the motion initially resulted in a tie, until the Panel Chair voted in favor of the motion. The conditions were then elaborated as follows:

- 1) The labeling should reflect specific contraindications and inclusion and exclusion criteria such as restrictions on patients with a Hutch diverticulum, dysfunctional voiding, neurologically impaired bladders, and nonfunctioning

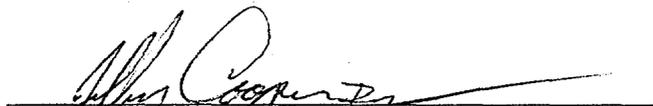
kidneys, and other changes as reflected in the discussions. Informed consent on Grade IV should be required, and information on alternative treatment options should be included. The need for antibiotic use until reflux is gone should be noted, and statistics with respect to age, gender, and degree of reflux treated should be included, as should comparison with spontaneous remission rates. The risk of UTI should be discussed. This condition passed.

- 2) A prospective postmarketing study should be conducted at several sites in the United States with multiple physicians and sufficient number of patients to show efficacy in age and gender subsets. Efficacy should be addressed and stratified by age, gender, grade of reflux, race, number of treatments, and other specifics to be determined by the FDA. Effectiveness should be defined as zero reflux. The control could be historical data on the nontreated population. This condition passed.
- 3) During the premarket period, more long-term data should be collected in Studies 1,2, and 3 in terms of efficacy to provide a better picture of device performance. Data should be collected on the numbers of those reimplanted and those with other surgical procedures. If these data meet FDA satisfaction, the information can be brought to a committee, subcommittee, or panel consultants as homework assignments to negotiate labeling. If the European data are satisfactory, then an additional postmarket U.S. multicenter study can be done, with the U.S. data to be included later in the labeling. This condition passed.

The motion to recommend the PMA as approvable subject to the specific three conditions described above carried by a vote of four to two.

Panel Chair Dr. A. Kalloo thanked the panel, the sponsors, and the FDA and adjourned the session at 3:30 p.m.

I certify that I attended the Open Session of the Gastroenterology and Urology Devices Advisory Panel Meeting on October 19, 2000, and that this summary accurately reflects what transpired.



Jeffrey W. Cooper, D.V.M.
Panel/Executive Secretary

I approve the minutes of this meeting as recorded in this summary.



Anthony N. Kalloo, M.D.
Panel Chair

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