

INTERGEL® Adhesion Prevention Solution

CLINICAL EXPERTS CONSENSUS REPORT ON SAFETY AND EFFECTIVENESS

April 29, 2001

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INTRODUCTION

Postsurgical adhesions are a highly prevalent complication of abdominal and pelvic surgery, generating significant morbidity. In major gynecologic surgery, post-operative adhesions are estimated to occur at a rate of 60-90% (Monk et al. 1994), with at least 15-20% of female infertility cases attributed to pelvic adhesions (Milingos et al. 2000b, Drollette and Badawy 1992). Postsurgical adhesions are the largest single cause of intestinal obstruction. From 30 to 41% of bowel obstruction surgery is due to adhesions, with 65-75% of these cases in the small bowel (Menziez 1993; Ellis 1998). Some cases of chronic pelvic pain are likely to be attributable to postsurgical adhesions, based on data from 11 studies in which this was the most common pathology observed (40% of cases) (see Holmdahl et al. 1997). However, well-designed studies in support of pelvic pain as a complication of postsurgical adhesions are lacking to date.

The impact of adhesions as a common and long-term complication of surgery places an enormous burden on patients, surgeons, and health care resources. A conservative estimate based on data from the National Center for Health Statistics indicates that over 7 million abdominal and pelvic surgeries are conducted annually in the US (NCHS 1998), the vast majority of which could be expected to result in cases with postsurgical adhesions (Menziez and Ellis, 1990). There are more than 3 million open gynecologic surgeries annually and an estimated 400,000 surgeries in women for peritoneal adhesiolysis each year (NCHS, 1998).

Utilizing the medical record linkage database of the Scottish National Health Service, the impact of postsurgical adhesions on public health has been recently assessed with notable rigor. It was determined that 5.7% of all hospital readmissions in this cohort (21,347 cases) over ten years were directly related to adhesions, with 3.8% of these cases managed operatively. Although 22% of readmissions occurred in the first year, readmissions continued steadily over the 10 year follow-up period. (Ellis et al. 1999). For open gynecologic surgery (8,489 cases), nearly 50% of re-admissions were for surgeries that could potentially be complicated by the presence of adhesions. 4.5% of readmissions were directly related to adhesions, and 34.5% of patients were readmitted an average of 1.9 times for a problem related to adhesions, or for further intrabdominal

INTERGEL® Adhesion Prevention Solution
CLINICAL EXPERTS CONSENSUS REPORT
April 29, 2001

surgery that could be complicated by adhesions. As with the larger cohort, readmissions directly related to adhesions in the open gynecologic surgery population continued throughout the 10 year follow-up (Lower et al. 2000).

The only treatment for symptomatic postsurgical adhesions is surgery. There is an urgent need for adjuvants to prevent or reduce the risk of postsurgical adhesions. Methods currently employed are limited to good surgical technique¹ and two products for site-specific adhesions. No products are available in the U.S. as adjuvants for non-surgical site adhesion prevention.

REVIEW AND ANALYSIS OF DATA ON SAFETY AND EFFECTIVENESS OF INTERGEL® ADHESION PREVENTION SOLUTION (INTERGEL®)

The panel members independently, and subsequently jointly, reviewed the data submitted to the Food and Drug Administration in support of marketing approval for INTERGEL® Adhesion Prevention Solution (INTERGEL®). This information included the Premarket Approval Application (PMA) as amended (June 2, 2000), along with relevant published literature, and case report forms from the pivotal trial. To illuminate and duly consider the scientific and clinical concerns expressed by FDA and the previous Advisory Panel with regard to this product, the panel considered the proceedings of two FDA Advisory Panel meetings (one meeting convened to review the INTERGEL® PMA prior to amendment; a second to consider the standards for approval of barriers for adhesion prevention); and FDA correspondence and meetings with the sponsor (including the not-approvable letter issued November 15, 2000; minutes of meetings held with FDA on October 27, 2000 and December 14, 2000).

INTERGEL® is an isotonic, viscous solution of sodium hyaluronate which has been ionically cross-linked with iron. The results of the first clinical study of this product in 23 patients (peritoneal surgery via laparotomy, with subsequent laparoscopy) identified no safety concerns, and provided preliminary evidence of effectiveness (Thornton et al. 1998). The pivotal trial to evaluate the safety and effectiveness of INTERGEL® was a multi-center, randomized, prospective, blinded, controlled trial in women undergoing pelvic gynecological surgery via laparotomy. Adhesions were directly assessed at this initial surgery at 24 sites in the peritoneal cavity, followed by direct assessment from 6 to

¹ Delicate handling of tissues; good hemostasis; minimizing or avoiding the introduction of foreign materials, such as powder on gloves and the minimal amount of suture material; excision of abnormal tissues; precise alignment and approximation of tissue planes; pelvic lavage; and minimally invasive approaches.

INTERGEL[®] Adhesion Prevention Solution
CLINICAL EXPERTS CONSENSUS REPORT
April 29, 2001

12 weeks later via laparoscopy.² The methodology used to assess adhesions, based on the American Fertility Society (AFS) scoring system, was uniform and standardized, providing data on incidence, severity, and extent of adhesions at 24 sites during both invasive procedures in a blinded manner.

Results of this pivotal trial provide adequate evidence to conclude that the product is effective in reducing non-surgical site adhesions, reformed adhesions, and adhesions at the surgical site. The trial data also confirm that the product is safe, with no adverse events (including infection) occurring at a higher rate in the treated group than in the control group. The safety of the product is also supported by appropriate nonclinical studies, and the panel notes that sodium hyaluronate has been safely used in surgical applications for decades.

The INTERGEL[®] PMA as amended has not yet been the subject of an FDA Advisory Panel review. As such, the present panel was requested to consider the data in this submission, and the extent to which the data provided in the revised PMA adequately resolve scientific and clinical issues raised by FDA and the previous Advisory Panel (January 12, 2000). Based upon the not-approvable letter issued November 15, 2000, it is assumed that the issues of concern to FDA (and the original panel) are: validity of the study design and data; validity of the methodology for assessing adhesions; the clinical significance (impact on medical care) of the effectiveness results; and the potential for an increased risk of infection.

The revised intended use proposed by the sponsor for INTERGEL[®] is as follows:

INTERGEL[®] Solution is a single-use, intraperitoneal instillate indicated to reduce the likelihood of developing moderate or severe postoperative adnexal adhesions in patients undergoing adhesiolysis or myomectomy during conservative gynecological pelvic surgery by laparotomy, when used as an adjunct to good surgical technique. INTERGEL[®] Solution was also shown to reduce adhesion reformation to sites in addition to the adnexa, and adhesion formation at surgical sites, including the anterior abdominal incision.

Without question, adnexal adhesions impair fertility. This conclusion is based on decades of clinical experience and over 20 specific studies in the clinical literature that correlate the incidence, extent and severity of adhesions on the fallopian tubes and ovaries to measures of fertility status (e.g. Nagata et al., 1997a; 1997b; 1998; Gomel and Erenus, 1990, Mage et al. 1986, Marana et al. 1995, Milingos et al. 2000a). On that basis alone, the data provided by the Sponsor resolves the question of clinical utility for this

² This trial, designed in 1995, could likely not be conducted in the U.S. today due to the lack of patients for whom a second-look laparoscopy would be medically indicated, the increasingly common use of *in vitro* fertilization, and a decline in the number of open laparotomies in favor of less invasive surgical approaches for some surgeries.

INTERGEL[®] Adhesion Prevention Solution
CLINICAL EXPERTS CONSENSUS REPORT
April 29, 2001

product. It is recognized that the AFS score in the INTERGEL[®] trial was calculated from observations at 3 sites on the ovary and 2 sites on the fallopian tubes. This calculation was not retrospective, but appeared in the original trial report. Some members of the present panel participated in the arduous process of developing the AFS score (R. Malinak, L. Mastroianni). Based on physiological and anatomical considerations, coupled with statistical tests for sensitivity, we conclude that this assessment of adnexal adhesions by the Sponsor is reasonable and valid.

The changes observed in AFS scores for patients from baseline to second-look (so-called "shift scores") were statistically significant and clinically meaningful. Patients in the control group were more likely to have moderate to severe adnexal adhesions than the treated group (13% vs. 2%). This represents a relative risk of 0.195, or a 5-fold difference in risk. Patients with moderate to severe adnexal adhesions have little to no likelihood of natural conception. The effectiveness of the product in reducing the risk of adnexal adhesion formation was observed for all patients and sub-groups of surgical procedures in the trial (myomectomy; adhesiolysis; tubal procedures; ovarian procedures). The number of patients positively affected on the basis of AFS scores alone, is a significant segment of the study cohort. This number, approximately 10% of the study population, is reasonably assumed to represent the most conservative estimate of the product effectiveness, since the baseline adhesion scores in both the control and treatment arms are lower than what one typically observes outside of a clinical trial setting. Even if the product generated this magnitude of change in a similar percentage of gynecological surgery cases postmarketing, the absolute number of women who would derive a clinically meaningful benefit from the product would be very large.

In addition to the adnexal adhesion results, the effectiveness of the product as an adhesion prevention adjunct is reinforced by the statistically significant differences observed in other measures of adhesion incidence, notably reformed adhesions (31% reduction), and *de novo* surgical site adhesions (24% reduction). The magnitude of these reductions are also clinically important and comparable to those observed for previously approved site-specific adhesion prevention products. The panel notes that the original presentation of the INTERGEL[®] pivotal trial data, in which the assessment of adhesions at all 24 abdominal and pelvic sites are considered, provides more robust support for the effectiveness of the product.

The panel evaluated the safety of the product, as presented in nonclinical studies, the feasibility trial (Thornton et al. 1998) and the pivotal trial. No safety concerns were identified. The question of whether or not INTERGEL[®] poses an infection risk was considered in depth by the panel in response to the analysis of this issue presented by FDA to the Advisory Panel (January 2000) and to the Sponsor (not-approvable letter dated November 15, 2000). Two complete independent reviews (S. Faro, J. Sever) of all data, including case report forms were conducted by two members of this panel (S. Faro, J. Sever), followed by consideration and discussion of their findings by all members.

INTERGEL® Adhesion Prevention Solution
CLINICAL EXPERTS CONSENSUS REPORT
April 29, 2001

Postoperative pelvic infections or wound infections following the surgical procedures performed on the INTERGEL® trial (myomectomy procedures; excision of ovarian endometriomas; adhesiolysis) would be due primarily to exogenous bacteria. The myometrium and endometrium tend to be sterile sites; in the surgeries performed it is not likely that vaginal microflora would have access to, or be present in sufficient amounts, to produce an infection. Wound infections are commonly caused by *Staphylococcus aureus*. Risk factors for postoperative infections are: abnormal vaginal microflora; underlying chronic disease; hematoma at the surgical site; seroma at the surgical site; necrotic tissue; presence of a foreign body at the surgical site; and interruption of the vascular supply (Faro and Soper 2001).

The anticipated rate of infection for "clean" surgeries cited as 1% by FDA is not considered by this panel to be directly applicable to the procedures performed in this study. The anticipated infection rate for gynecological surgeries has been variously reported as 2.4% (Howard 1999) and 3.3% (Hager 1997). The panel considers these to be conservative estimates.

As noted previously, the rate of postoperative infections was comparable in the INTERGEL® group compared to control (lactated Ringer's solution). Drs. Faro and Sever independently assessed the entire data set to identify cases of wound infection, pelvic infection, or febrile morbidity applying clinical judgement to specific criteria for the diagnosis of each case. The diagnostic criteria for wound infections are: fever, elevated white blood cell count, elevated pulse rate, erythema, induration, pain, and purulent drainage. The criteria for diagnosis of pelvic infections are: fever, elevated white blood cell count, uterine tenderness, pelvic peritonitis, decreased bowel sounds, and ileus. The diagnosis of febrile morbidity, a common postoperative event and distinguished from infection, is based on: fever, normal pulse rate, normal white blood cell counts, and normal bowel sounds.

Given these criteria, Dr. Faro's assessment resulted in a rate of infection *possibly* related to treatment of 2.1% in the INTERGEL® group, compared to 2.2% in control (3 cases vs. 3 cases). Dr. Sever's assessment resulted in a rate of infection *possibly* related to treatment of 2.8% in the INTERGEL® group compared to 2.2% in the control group (4 cases vs. 3 cases). In both independent assessments, there was no statistically significant difference in the infection rate observed in the INTERGEL® group compared to control. The statistical analysis applied by this panel, and by the Sponsor (Fisher's exact test), is appropriate for comparing adverse event rates in a randomized trial, including the rate of infection. In both assessments, neither Dr. Faro nor Dr. Sever found any cases of postoperative infections of any type to be *definitely* related to exposure to the test article or control, a finding in accord with the original assessment of the clinical study investigators.

The panel agrees with the in-depth assessment of cases conducted independently by their colleagues, Drs. Faro and Sever, namely, that no statistically significant difference or

**INTERGEL® Adhesion Prevention Solution
CLINICAL EXPERTS CONSENSUS REPORT
April 29, 2001**

clinically meaningful difference in infection rates was observed in the two arms of this trial. Other potentially significant postoperative events were absent in both arms: pulmonary edema; electrolyte imbalance; immunosuppression; and anuria. The panel also noted that the concern of an infection risk posed by INTERGEL® has not been borne out in the postmarketing experience. The product is marketed in 25 countries. With approximately 25,000 units sold, there have been no reportable adverse events of any type.

It is unfortunate that the FDA Advisory Panel who reviewed these data in January of 2000 were not aware of the nature of the individual cases reported as "infection." The slide presented by FDA, accompanied by the statement that the infection rate was "higher" in the INTERGEL® group, did pose cause for concern. However, in the discussion of these data by the previous Advisory Panel it was apparently unclear that the numbers between the two groups were not statistically significant, nor that the numbers presented included cases of chicken pox and a "head cold." Other infections that occurred in both groups that cannot be attributed to either INTERGEL® or lactated Ringer's are upper respiratory tract infections, cystitis, and urinary tract infections.

CONCLUSIONS

This panel agrees unanimously that sufficient reliable data has been provided to support the conclusion that INTERGEL® is an effective adjunct for the reduction of postsurgical adhesions in gynecological surgery. Intense scrutiny of this data has failed to reveal any clinically meaningful safety concerns. The design of the trial, the nature of the endpoints assessed, the magnitude of the adhesion reductions observed, and the numbers of patients positively affected, are sufficient to establish that the numerous measures of statistically significant differences observed are clinically significant and medically meaningful. The panel did not identify any new clinical or scientific issues of concern.

The panel, having considered the specific questions following independent and joint review of the data, answered as follows.

- 1. Does the design and analysis of the INTERGEL® Adhesion Prevention Solution pivotal clinical trial provide reliable and valid scientific evidence to support conclusions regarding safety and effectiveness for the proposed intended use?**

Please consider: endpoints evaluated; method for assessing adhesions; magnitude of differences observed between treatment and control; clinical significance of study and findings.

Yes. The study design, execution, and analysis provides valid and reliable data sufficient upon which to base conclusions in support of the proposed intended use.

INTERGEL® Adhesion Prevention Solution
CLINICAL EXPERTS CONSENSUS REPORT
April 29, 2001

The panel notes that adhesions are a complication of surgery and as such are a suitable primary endpoint for evaluating the effectiveness of an adjunct in support of approval. As a supplemental consideration of this issue, the panel developed alternative study designs in which bowel obstruction, pain, or pregnancy were the primary measure of effectiveness. It was concluded from careful consideration of these clinical protocols that such studies are not feasible due to ethical, methodological, and logistical constraints. Small bowel obstruction studies (after abdominal surgery or gynecological surgery) would require sample sizes from 12,000 to 45,000 (respectively), and from 5 to 9 years from study initiation to completion (follow-up of 3 years). These numbers are conservative estimates which assume only a 10% loss to follow-up. Pregnancy as a primary endpoint for an adhesion prevention trial in either abdominal or pelvic surgery patients has the advantage of an objective endpoint and a larger event rate than small bowel obstruction. However, given the multi-factorial etiology of fertility, the panel concludes that accruing a study population to minimize confounding factors would likely require many years. Further, such a study would likely be unethical, given the availability of *in vitro* fertilization. For the same reason, the study design could not include randomization.

The event rate for pain following abdominal or pelvic surgery is not known, nor is there consensus on the manner in which this outcome should be assessed or methods to control for the multi-factorial nature of the problem.

2. Is the product safe, as defined by FDA regulations 21 CFR 860.7(d)(1):

“There is reasonable assurance that a device is safe when it can be determined, based on valid scientific evidence, that the probable benefits to health under the conditions of intended use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks.

The valid scientific evidence used to determine the safety of a device shall adequately demonstrate the absence of unreasonable risk of illness or injury associated with use of the device for its intended uses and conditions of use.”

Yes. The evidence provided is reasonable and sufficient to conclude that the benefit of INTERGEL® use for the labeled indications outweighs any probable risks, and the Sponsor has provided valid scientific evidence to demonstrate that the product does not pose an unreasonable risk of injury or illness.

3. Is the product effective, as defined by FDA regulations 21 CFR 860.7(e)(1):

“There is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target

INTERGEL® Adhesion Prevention Solution
CLINICAL EXPERTS CONSENSUS REPORT
April 29, 2001

population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.”

Yes. The evidence provided is reasonable and sufficient to establish that the product is effective, and that the nature, extent, and magnitude of the reductions observed are clinically significant. The absolute number of patients positively affected is a significant portion of the study population.

4. What labeling considerations or other conditions, if any, would you recommend as requirements for approval and marketing of INTERGEL®?

None. The proposed label for this product is adequately supported by the data provided in the PMA as amended. The studies and analysis provided are sufficient and valid evidence in support of safety and effectiveness.

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INTERGEL® Adhesion Prevention Solution
CLINICAL EXPERTS CONSENSUS REPORT
April 29, 2001

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**INTERGEL® Adhesion Prevention Solution
CLINICAL EXPERTS CONSENSUS REPORT
April 29, 2001**

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PANEL MEMBERS

Panel members were recruited for their clinical and research expertise in obstetrics and gynecology, specialization in reproductive medicine and surgery, infectious diseases (particularly in gynecological surgery), research experience in adhesion prevention, pathogenesis and/or clinical management, and substantial leadership positions in their field, as evidenced by peer-reviewed publications, textbooks, professional society positions, editorial boards, and academic appointments.

One panel member (R. Malinak) was an investigator in the INTERGEL® pivotal trial. A second panel member (M. Martens) was listed as an investigator but his site did not accrue subjects. Curriculum vitae for each panel member is appended (Appendix I)

Alan H. DeCherney (hs 5/17/01)

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INTERGEL® Adhesion Prevention Solution
CLINICAL EXPERTS CONSENSUS REPORT
April 29, 2001

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INTERGEL® Adhesion Prevention Solution
CLINICAL EXPERTS CONSENSUS REPORT
April 29, 2001

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