

OB-Gyn Clinical Summary Memo

SUBJECT: LIFECORE BIOMEDICAL, INC., INTERGEL® ADHESION PREVENTION SOLUTION,
P990015/A011

INTRODUCTION

The General Surgery Division of the Center is reviewing Intergel® Adhesion Prevention Solution. The sponsor presented the device and the pivotal trial results at a panel meeting in January. The panel did not recommend approval based on inadequate safety data and inability to show effectiveness. Since then, the sponsor has re-evaluated the data. This amendment contains a new endpoint for evaluation and a new indication for use for our consideration.

Before beginning, it is important to remember that the statistical evaluation of the data assumed that the study would be an intent to treat study. In addition, a difference of two points per patient in the population (Modified AFS score) would be statistically significant. At the panel meeting, the panel agreed that a difference of two points in mAFS adhesion score was not clinically significant regardless of the statistical conclusions.

INTENDED USE

Revised Indication for Use- 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.

Previous Indication for Use- Intergel® Solution is indicated for use as a single use, intraperitoneal instillate for reduction of adhesions following gynecological pelvic surgery. It has been shown to reduce the incidence, extent and severity of post-surgical adhesions throughout the abdominal cavity when used as an adjunct to good surgical technique during laparotomy procedures.

PANEL DELIBERATION

Below are the essential issues the panel felt the Intergel® Solution pivotal trial did not address.

1. The first was safety. The sponsor failed to perform an important animal infectivity study before coming to panel. In addition, as one panel member noted the infection rate for the patients receiving Intergel® was 3.9% compared to 1% for those who did not. This result was statistically not significant. However, there could be significant clinical consequences to doubling the infection rate in a population of patients interested in fertility. Therefore, The panel felt that the safety of this device was not completely resolved.
2. The second issue was effectiveness. The study had to show a clinically meaningful effect from the device. The panel understood clinically meaningful reduction in adhesion load as being a large difference in adhesion scores between the treatment and control population. Again, the sponsor was only able to show a difference of less than 2 adhesions between the test and control groups.

REVIEW OF SPONSOR SUBMISSION

The sponsor has tried to address these two concerns. The sponsor did conduct the safety study mentioned. The results showed no increase in mortality when the device was used in the presence of fecal contamination. The infection rate in the study has not been discussed.

To address effectiveness, the sponsor chose a new endpoint and presented data to support it. In addition, the sponsor changed the indications for use as shown above. They present the indication for use and then discuss how, in the context of this new endpoint the indications are justified. I will organize my discussion of their results and conclusions in the same manner.

“INTERGEL® SOLUTION IS A SINGLE-USE, INTRAPERITONEAL INSTILLATE INDICATED TO REDUCE THE LIKELIHOOD OF DEVELOPING MODERATE OR SEVERE POSTOPERATIVE ADNEXAL ADHESIONS...”

The AFS score as originally developed by the American Society for Reproductive Medicine (ASRM, formerly the American Fertility Society-AFS) is the basis for the above statement. The sponsor has calculated AFS scores for each patient as the new endpoint. The sponsor presents research done by 5 investigators to support the clinical utility of this scoring system. According to the sponsor, the articles support the conclusion that women with moderate/severe (two of the AFS score categories) adhesions fare worse clinically than women with minimal/mild (the other 2 AFS categories) disease. Thus, although the adhesion score leads to one of four categories in truth only two categories are clinically relevant. Before discussing the results of the pivotal trial, I will spend a few paragraphs discussing the articles and the AFS scoring system.

The original article about the AFS score simply presented the system as a standardized way to score adhesions to allow for comparisons between adhesion investigations. Of the 7 articles they present, they conclude that 5 of the articles support the use of the score, one article shows that the score may be helpful prognostically and another does not support the use of the scoring system. The following is a more detailed analysis of the articles presented for proof of clinical validation of the AFS score. I will not present the article by Marana (1995) since the sponsor states that it does not support the claim that the AFS classification system is prognostic.

The AFS score was published in 1988. Mage published his article in 1986. The scoring system scores the tube as two separate parts. The AFS score evaluates each tube in its entirety. The study was prospective and performed with 76 patients. Twenty-seven patients became pregnant with 20 intrauterine pregnancies. This study looked at both adhesion and tubal scores (obtained by salpingoscopy). The authors found that severe adhesions were predictive of poor pregnancy outcome but minimal, mild and moderate were all the same.

Gomel presented an abstract at the ASRM meeting in 1990 (then called the AFS). Prospective evaluation of ninety women was performed. Seventeen had mild disease and 73 had severe disease. The AFS score was used to score the adnexal adhesions. There was a difference in the intrauterine pregnancy outcome in the patients with mild disease as compared to severe disease.

DeBruyne (1997) looked at 226 women prospectively. He divided the women into patients with and without tubal obstructive disease. In addition, only the tubal adhesions were scored. The adhesion score was compared to the tubal score obtained at the same time. This is not the standard

way to perform the AFS, dividing patients into obstructive and non-obstructive tubes and scoring only the tubes.

Nagata has published three articles on scoring systems for infertile patients. I was able to obtain two of the three articles cited in A010. The first 1997a, is presented in Human Reproduction. This study looks at the predictive value of peri-ovarian adhesions alone. Successful IVF procedures are the endpoints. It does not use the AFS scoring system in its entirety.

The second presentation by Nagata was a poster at the 1997 ASRM meeting. The poster presented an alternative scoring system to the AFS score. The alternative system divided the tubal and ovarian adhesions into two separate categories. Nagata showed that severe peri-tubal adhesions would require intervention for pregnancy while mild, minimal, and moderate adhesions would not. Severe peri-ovarian adhesions were predictive of poor pregnancy rates and success with IVF procedures. Again, this is not the AFS score but a revision of the original system.

The timing of the scoring is another issue not addressed in these studies. At the beginning of the first surgery is when the investigators score the adnexa. This means that the predictive value of a second look score, which was the endpoint for this study is unknown.

In summary, these articles present some evidence that severe adhesions as opposed to minimal, mild and moderate may decrease the likelihood of pregnancy in infertile patients. However, the AFS score might not accurately record the disease since it combines the ovarian and tubal scores and many of the articles separated these two scores. The sponsor argues that grouping the patients into mild/minimal and moderate/severe categories gives accurate information as to the prognosis of the patient's disease. This claim is not borne out by these studies. In addition, none of these studies address the second look scores only the scores done at the time of the original surgery so the clinical validation of the second look scores is still in question.

Before I discuss the results, I should say a word about how the sponsor calculated the AFS score for women in this study. In the scoring system (the mAFS score looking at the density and extent of adhesions at 24 sites around the pelvis and abdomen) used during the study, the investigator scored six separate areas for each tube and ovary. Note that for the AFS score the tube and ovary are scored as one site each. To obtain an AFS score, scores from the six sites are condensed into the AFS scores. The scores from the original system were averaged and recategorized to fit the AFS criteria. There is no precedent for this method of obtaining an AFS score. Therefore, I am concerned that the scores are not in fact, the true AFS scores of the adnexae.

The other change the sponsor made was to impute the data. Originally, the study was designed as an intent to treat study. However, in the original PMA presentation the sponsor only presented the evaluable patients. An intent to treat analysis was performed by the sponsor during the review process and it showed no statistical difference in the endpoints between the test and control groups. As a compromise in this amendment the sponsor has imputed the data, adding back only a portion of the lost to follow up patients.

For the claim quoted above, only a subgroup of the entire patient population is needed to understand the results. For the evaluable, intent to treat and imputed data the subgroup is the same. It is a condensed version of table 5.12 in A011 and table 8.2a in A070. The table presented here looks only at the difference in minimal and severe disease since this is the most their literature search

in support of the AFS can support. Please remember that prognostic significance of the second look score was not supported by the articles presented.

The women with minimal disease represent the majority of the patients in the study. As demonstrated in this table only a small number of them go on to develop severe adhesive disease after one procedure. With such a small number of patients of interest in this study, it is impossible to state definitively that this device will be of benefit. Also when reviewing this table, please remember that the original study excluded women who had more than half of the sites identified in the mAFS scoring system involved with adhesions. Several protocol violations allowed these women into the study anyway. The patients with severe disease at first look in this table were most likely protocol violations making this group extremely biased. As presented in the 11th amendment as well as the table below, the inclusion of the patients with severe disease is what makes the difference between the treatment and control groups statistically significant.

| Category | Baseline total Intergel | Minimal 2 nd look Intergel | Severe 2 nd look control | Baseline total control | Minimal 2 nd look control | Severe 2 nd look control |
|----------|-------------------------|---------------------------------------|-------------------------------------|------------------------|--------------------------------------|-------------------------------------|
| Min | 109 | 103 | 1 | 109 | 96 | 4 |
| Svr | 2 | 2 | 0 | 4 | 2 | 1 |

In summary, in order to make the claim bolded above the sponsor had to validate the AFS criteria and then present compelling evidence that the use of the device lowered the second look AFS scores in such a way as to be clinically beneficial to the patient. The articles they presented do not conclusively support the clinical validity of the AFS score and they do not discuss the clinical validity of a second look score. The AFS score for the study patients is derived mathematically and not by the traditional method. There are too few patients of interest to make any conclusive statements about the patients with minimal disease who develop severe disease. The data on patients with severe disease is on a very small subset and biased.

“...IN PATIENTS UNDERGOING ADHESIOLYSIS OR MYOMECTOMY DURING CONSERVATIVE SURGERY BY LAPAROTOMY, WHEN USED AS AN ADJUNCT TO GOOD SURGICAL TECHNIQUE. ...”

Before proceeding with the data analysis, I should say that the panel statistician, Dr. DeMets did not believe that the number of patients in this study could support subgroup analysis.

Table 5.14 in A011, presents the data in support of this statement. It is from subgroup analyses of the different surgical populations. There were 88 patients who underwent myomectomy in the test group and 92 in the control. There were 66 test patients who underwent adhesiolysis and 65 in the control. Note some patients might have had myomectomy and adhesiolysis, presumably they are counted twice.

Again, when looking at adhesiolysis it is difficult to include the women who had severe disease at first look since they should've been excluded and they bias the results. This table also divides the patients into min/mild and mod/svr which may not be the correct classification. When we review

table 8.2b from A7, p33 that presents the pre-reconciliation, intent to treat patient population and focus just at the women with minimal disease the difference between test and control population disappears.

The myomectomy group is more difficult to understand. Several factors must be considered such as adhesiolysis that occurred during the surgery and number of incisions made on the uterus at the time of the procedure. Both of these will affect the adhesion formation rate post-operatively. Neither is discussed in this submission.

In summary, we have two subgroups presented. When evaluated as the study design intended, regardless of endpoint there is no difference in adhesion formation. In addition, there is inadequate information about the myomectomy patients.

“...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.”

This final section refers to original scoring system used to evaluate adhesions during this pivotal study. The data on reformed adhesions and surgical site adhesions showing statistical significance as presented here was based on the evaluable patient population which did not include lost to follow up. The original statistical plan was based on an intent to treat population. The statistical significance of this data disappears when the calculations are based on the appropriate population (see oral presentation by Richard Kotz, statistician at the January 20, 2000 panel meeting). Regardless, from a purely clinical perspective, the change of 0.94 for reformed and 0.69 for surgical sites (as shown in A010) is insignificant once one realizes that the overall scale is from 0-32.

COMMENTS

The additional infectivity study was performed and showed no increase in mortality. However, as noted in the panel meeting the infection rates for test and control populations were different, the rate was increased for the test group. This finding may warrant further study.

The AFS score is a way of classifying adnexal adhesions, it is not accepted in the clinical community as a prognostic indicator. The sponsor presented some evidence that there is a difference in clinical endpoints between women with severe and women with minimal adhesive disease. The study was not designed to study this population (women who developed severe adhesive disease after one surgery. In addition, there is no information on the use of the AFS score for prognosis, when used at the second look surgery. Finally, the AFS score was not obtained in the standard manner during this study and may make the results inaccurate.