

**SECTION II.**

**PROPOSED INDICATIONS FOR USE (*REVISED*)**

## PROPOSED INDICATIONS FOR USE (*REVISED*)

The original PMA for INTERGEL® Adhesion Prevention Solution (P990015) contained the following proposed indication for use. It was based on the effectiveness data gathered in the pivotal trial from a systematic evaluation of the incidence, extent and severity of post-surgical adhesions at 24 sites assessed at second-look. The proposed alternative is supported by a subset of the same data, inclusive of all patients but not all sites evaluated. The modified label reflects a commitment to restrict the efficacy claims regarding adhesion prevention to (1) those sites scored utilizing a validated method to relate the extent and severity of adhesions to clinical outcomes, and (2) those sites scored for which there is substantial clinical justification (and regulatory precedent) for approval.

### **Originally Proposed:**

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.

### **Revised:**

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.

### **Data in Support of the Revised Label:**

*"INTERGEL® Solution is a single-use, intraperitoneal instillate indicated to reduce the likelihood of developing moderate or severe postoperative adnexal adhesions . . . "*

See data presented in Section III (page 41):

#### **5.2.2.2 Shift Tables: Primary Analysis Presented as Success/Failure**

A moderate or severe AFS adhesion score at second-look was considered a treatment failure in this study. Table 5.12 presents baseline and second-look results for all four AFS adhesion categories (upper part of table), followed by the analysis of treatment success/failure (binary analysis, lower part of table).

As indicated, 109 patients in the INTERGEL® Solution group had a baseline AFS adhesion score in the minimal category. Of these, 103 remained in the minimal AFS category at second-look, while 4 became mild, and 1 each became moderate and severe. In the control group, 109 patients also had a baseline AFS score in the minimal category, but fewer (96) of the 109 patients remained in the minimal category at second-look, while 6 became mild, 3 became moderate and 4 became severe. Analysis using the Cochran-Mantel-Haenszel test controlling for baseline level indicates a highly significant p value ( $p = 0.001$ ) between treatment groups in the shift of patients from one AFS adhesion category to another.

In the analysis of treatment success/failure (binary analysis), 3 of 122 INTERGEL® Solution patients (2.5%) shifted from the minimal/mild category to the moderate/severe category compared to 10 of 117 control patients (8.5%). All nine patients in the INTERGEL® Solution group (100%) that started off in the moderate/severe category improved (moved to the minimal/mild group) compared to only 10 of 17 control patients (59%). Analysis using the Cochran-Mantel-Haenszel test controlling for baseline level indicates a highly significant p value ( $p = 0.003$ ) with regard to the difference in treatment success/failure. Overall, 3 patients in the INTERGEL® Solution group (2.3%) had moderate or severe adhesion scores at second-look, compared to 17 (12.7%) patients in the control group. Based on these data, the relative risk of treatment failure in the control group is 5 times that of the INTERGEL® Solution group.

*"... in patients undergoing adhesiolysis or myomectomy during conservative gynecological pelvic surgery by laparotomy, when used as an adjunct to good surgical technique. ..."*

See data presented in Section III (page 45):

#### **5.2.2.4. Subgroup Analysis by Surgical Procedure**

A subgroup analysis by surgical procedure indicates that those patients most likely to benefit from INTERGEL® Solution were those undergoing adhesiolysis and myomectomy procedures as shown in Table 5.14. For those patients who underwent myomectomies, the percentage of treatment failures (patients with moderate or severe adhesions at second-look) was significantly reduced from 9.8% to 2.3% ( $p=0.036$ ) in the INTERGEL® Solution group. The percentage of patients with treatment failures (moderate to severe adhesions at second-look) was significantly reduced from 20.0% to 3.0% ( $p=0.006$ ) in the INTERGEL® Solution group for patients undergoing adhesiolysis procedures. Patients who underwent tubal procedures, ovarian procedures, and ablation of endometriosis also showed favorable trends with INTERGEL® Solution.

*"... 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."*

See data presented in Section III (page 47):

### **5.2.3 Secondary Analyses**

In addition to the analysis of adhesion prevention based on the AFS adhesion score applied to the adnexa, analysis of surgical site adhesions and reformed adhesions were also included in the original report of this clinical trial, and are provided in this amendment as supportive evidence of efficacy.

#### **5.2.3.1 Proportion of Surgical Site Adhesions**

For each patient, the proportion of the surgical sites that had adhesions was determined at both baseline and at second-look laparoscopy, regardless of whether or not adhesions had been lysed at baseline (each patient had at least one surgical site, the site of incision). While the number of surgical sites was similar for the two groups at baseline (Table 5.9), the proportion of surgical sites with adhesions was significantly reduced ( $p=.003$ ) from 0.500 in the lactated Ringer's group to 0.386 in the INTERGEL® Solution group, a 23% reduction (Table 5.15).

#### **5.2.3.2. Proportion of Reformed Adhesions**

Similarly, the proportion of sites with reformed adhesions were assessed for each patient. Reformed adhesions were those that were lysed at first surgery that had reformed at second-look. While the number of adhesions lysed was similar for the two groups at baseline (Table 5.9), the proportion of sites with reformed adhesions was significantly reduced ( $p=.001$ ) from 0.663 in the lactated Ringer's group to 0.459 in the INTERGEL® Solution group, a 31% reduction (Table 5.15).