

SUMMARY OF SAFETY AND EFFECTIVENESS

I. General Information

Device Generic Name: Combined Hyperthermia and Chemotherapy Device

Device Trade Name: Synergo SB-TS 101.1 Device

Applicant's Name and Address: ME – Medical Enterprises
Odem 6
Petach Tikva
ISRAEL

PMA Number: P010045

Date of Panel Recommendation:

Date of Notice of Approval to the Applicant:

II. Indications for Use

The Synergo SB-TS 101.1 device delivers heat transurethrally by means of radio frequency (RF) energy to the urinary bladder walls. Synergo hyperthermia is delivered concomitantly with cooled intravesical instillation of Mitomycin C. Synergo treatment is intended for prophylactic treatment of recurrence in patients following endoscopic removal of Ta-T1 and G1-G3, superficial transitional cell carcinoma of the bladder (STCCB). Synergo treatment is clinically indicated for STCCB patients of intermediate and high risk.

III. Contraindications, Warnings and Precautions

Contraindications:

- Synergo treatment is contraindicated in patients whose pain response has been significantly decreased by any means (previous surgery or ionizing radiation therapy, general anesthetic, or other condition), as the patient's ability to detect pain is an essential safety mechanism.
- Synergo treatment is contraindicated in patients with cardiac pacemakers, as electromagnetic radiation from the Synergo antenna may interfere with the operation of an electronic device.

- Synergo treatment is contraindicated in patients with a single, TaG1 tumor at first episode of disease and patients with tumor stage greater than T1.
- Mitomycin is contraindicated in patients who have demonstrated a hypersensitive or idiosyncratic reaction to it in the past.

In addition:

- The Synergo should not be used under clinical conditions that preclude treatment administration (e.g., urinary tract infection, urethral stricture, fistula, partial cystectomy, previous pelvic irradiation therapy, bladder volume <150 ml).
- Febrile patients whose temperature is not in the range of 35.5 – 37.5°C (95.9 – 99.5°F) should not receive Synergo therapy.
- Mitomycin should be used with caution in patients with thrombocytopenia, coagulation disorder, or an increase in bleeding tendency due to other causes.

Warnings:

- Hyperthermia treatment can be safely and effectively administered only after careful placement of antenna and thermocouple devices as described in the User's Manual and with alert monitoring of tissue temperatures during treatment.

Precautions:

- The use of the Synergo device other than as specified in the indications, is limited by United States law to investigational use.
- To ensure accurate temperature monitoring during treatments, verify proper functioning of thermocouple devices as used.
- Monitor closely patients with metallic implants (e.g., joint prostheses) during treatment because such metal objects may be excessively (and preferentially) heated.

IV. Device Description

The Synergo SB-TS 101.1 device delivers heat transurethrally by means of radio frequency (RF) energy to the urinary bladder walls. Synergo hyperthermia is delivered concomitantly with cooled intravesical instillation of Mitomycin C.

Synergo is intended for prophylactic treatment of recurrence in patients following endoscopic removal of Ta-T1 and G1-3, superficial transitional cell carcinoma of the

bladder (STCCB). Synergo treatment is clinically indicated for STCCB patients of intermediate and high risk.

The Synergo SB-TS 101.1 device consists of the following two main components: (1) the hyperthermia device; and (2) the disposable catheter-tubing set.

The hyperthermia device consists of an operator console containing computer controls to obtain, display and record data from the thermocouple devices, RF directed and reflected energy, pressures in the tubing line, temperature of the heat exchanger and a means to display and record relevant patient treatment parameters. The computer controls enable the operator to control the treatment settings (i.e., RF energy and pump flow). The operator console contains the keyboard computer interface, computer monitor, computer and application specific software. The console also contains the drug circulating unit (heat exchanger, peristaltic pump and pressure transducer connectors).

The disposable catheter-tubing set consists of the following: a catheter system; and an interconnecting tubing line. The catheter system consists of the transurethral silicon catheter, 5 thermocouple devices and radiofrequency antenna device. It contains a radiofrequency antenna device for delivery of energy to the bladder. The catheter system also contains three thermocouples for monitoring bladder wall temperature, a balloon for positioning and anchoring the catheter against the bladder neck and provisions for drug delivery to the bladder. On the feeding cable of the antenna device, there are two additional thermocouples for measuring temperature on the feeding cable at the area of the prostatic urethra.

The interconnecting tubing line is used to connect the catheter to the drug circulating unit to provide a closed-loop drug circulating system. The drug circulating system includes external cooling of the chemotherapeutic solution and return circulation to the bladder. One section of the tubing line extends from the bladder, through the catheter lumen loaded with the bladder thermocouples to the heat exchanger. The other section of the tubing line brings the cooled solution from the heat exchanger to the bladder through the catheter lumen loaded with the antenna device and feeding cable thermocouples. In order to prevent the risk of overheating, the chemotherapeutic solution is continuously pumped out of the bladder and re-instilled after being cooled. This circulatory system is closed, thus allowing control of the temperature along the urethra and in the bladder.

The disposable catheter-tubing set is co-packaged with the MMC drug and supplied as the Synergo Kit. The Synergo device is a combination device/drug product.

V. Alternative Practices and Procedures

Approximately 70% to 80% of patients with newly diagnosed bladder cancer will present with superficial bladder tumors (*i.e.*, stage Ta, Tis, or T1). The major prognostic factors in carcinoma of the bladder are the depth of invasion into the bladder wall (Stage) and the degree of differentiation of the tumor cells (Grade).

The following treatment approaches exist for treating patients with cancer of the bladder:

- Surgery - eradication of the cancer by transurethral resection (TUR) or by cystectomy (segmental or radical cystectomy).
- Radiation therapy - uses high-dose x-rays or other high-energy rays to kill cancer cells and shrink tumors. Radiation therapy may be delivered by external radiation therapy or internal radiation therapy.
- Chemotherapy - uses drugs to kill cancer cells. Chemotherapy may be administered orally, by intravenous or directly into the bladder (intravesical instillation of chemotherapy). Chemotherapy given after surgery to a person who has no cancer cells that can be detected is called adjuvant or prophylactic chemotherapy.
- Immunotherapy – uses the body's immune system to fight cancer. It uses materials produced by the body or made in a laboratory to boost, direct, or restore the body's natural defenses against disease. Immunotherapy is administered directly into the bladder (intravesical immunotherapy).

Photodynamic therapy uses special drugs and light to kill cancer cells. A drug that makes cancer cells more sensitive to light is put into the bladder, and a specific wavelength is applied to the bladder. This therapy is being studied in clinical trials for early stages of bladder cancer.

Treatment of bladder cancer depends on the stage and grade of the disease, as well as the patient's age and overall condition.

The American Urological Association convened the Bladder Cancer Clinical Guidelines Panel to analyze the literature regarding available methods of treating nonmuscle invasive bladder cancer, and to make practice policy recommendations based primarily on treatment outcomes data. The results of this analysis were the American Urological Association Bladder Cancer Clinical Guidelines published in November 1999 in the American Journal of Urology and updated in December 2007².

The AUA guidelines recommend the following treatment: Mitomycin or BCG is appropriate for patients with “multifocal and/or large volume, histologically confirmed, low grade Ta or with recurrent low grade Ta bladder cancer.” For these same patients, maintenance BCG or MMC may be considered. Only BCG (with maintenance) is currently recommended for CIS and high-grade Ta or T1 disease.

VI. Marketing History

ME - Medical Enterprises obtained CE marketing approval of the Synergo device and disposable catheter-tubing set in 2000. The CE mark of approval was issued for the Synergo device when used in combination with a chemotherapeutic agent, for the prophylactic treatment of STCCB following complete eradication of the tumors and for

neo-adjuvant (ablative) treatment of STCCB. Health authority approval from the Israeli Ministry of Health was also granted in 2000.

No devices have ever been recalled or removed from the market due to device failure or adverse events.

VII. Potential Adverse Effects of the Device on Health

Although hyperthermia in conjunction with chemotherapy has the potential for producing a variety of adverse effects, those seen during the clinical investigation of the Synergo device were limited to direct effects of heating upon tissues and general side effects related to the hyperthermia and/or the chemotherapy treatment.

Anticipated Adverse Events:

Posterior Wall Tissue Reaction:

Posterior wall tissue reaction was experienced in 64% of the Study 101.1 patients, during the delivery of therapeutic heat by the local radio frequency antenna of the Synergo device. Posterior wall tissue reaction is a superficial (no muscle involvement), asymptomatic, transient event and is resolved without medical intervention and without significant residual effects.

Pain:

Pain was experienced in 40.5% of the Study 101.1 patients and in only 43 out of 426 (10%) of the total number of Synergo treatment sessions. Pain was localized and temporary during the delivery of therapeutic heat by the local radio frequency antenna of the Synergo device.

Other apparent side effects related to the Synergo treatment may include dysuria, hematuria, tissue reaction, urethral stenosis and skin allergy.

Other Adverse Events:

Reduced Bladder Capacity:

Two (4.8%) patients experienced reduced bladder capacity in Study 101.1.

Urinary Tract Infection:

Three (7.1%) patients reported urinary tract infection in Study 101.1. Adherence to recommended aseptic techniques during invasive placement of catheters may reduce the number of incidents.

False Passage:

One (2.4%) patient experienced false passage due to incorrect placement of the catheter, in Study 101.1. Adherence to recommended catheter placement techniques may reduce the number of incidents.

Hypotonic Bladder:

One (2.4%) patient reported a hypotonic bladder in Study 101.1.

Bladder Wall Necrosis:

Two (4.8%) of the patients reported bladder wall necrosis in Study 101.1. This may have been related to the direct effect of heat dissipation around the radio frequency antenna, or due to the effect of treatment on a residual tumor in the bladder.

VIII. Summary of Preclinical Studies

a. Laboratory Studies

The Synergo device was tested and conforms to the IEC 601-1 standard for mechanical and electrical safety. The Synergo device was tested and conforms to the IEC 601-1-2 standard for electromagnetic emissions and immunity compatibility. Software validation testing was also performed according to IEC 60601-1-4 and FDA guidelines.

The Synergo catheter was tested and complies with the requirements of the ASTM F 623-89 standard for Foley Catheters. Laboratory testing of the Synergo catheter also included testing for compliance with the ISO 10993 biocompatibility standard.

Bench testing included phantom tests to evaluate two aspects of the device; the electromagnetic field generated by the antenna and its interaction with simulated biological tissues. A correct estimate of the electromagnetic field shape permits the calculation of the energy generated around the antenna. Therefore, a direct electric field measuring system working in a liquid environment surrounding the antenna was developed. Secondly, a realistic phantom of the bladder was developed to estimate the tissue temperature rise during a simulated treatment. The specific absorption rate (SAR) was measured in a simple non-perfused phantom simulating the electromagnetic characteristics of the bladder. The SAR values were demonstrated to reach more than 100W/Kg in order to obtain effective hyperthermia over the desired treatment regions and decrease rapidly across the bladder wall.

A test was performed to determine the degradation of Mitomycin C dissolved in intravenous (I.V.) fluids, at 50°C (temperature higher than that used during Synergo treatment). In each of the sample preparations, the chemotherapy agent did not degrade below the approved Gensia Sicor Pharmaceutical bulk drug specification limits.

Paroni et al. (1) performed a study to assess the effect of Synergo on the systemic absorption of MMC during intravesical chemotherapy. These results demonstrate a statistically significant increase in the tissue permeability to MMC due to hyperthermia. The study demonstrated that the highest MMC plasma concentration occurred after 45 minutes of a Synergo treatment employing 40 mg MMC (indicated dosage). Despite the significantly higher systemic concentrations of MMC during intravesical instillation associated with hyperthermia, the systemic MMC

levels are still far below the systemic threshold toxic concentrations for myelosuppression of 400 ng ml^{-1} MMC, both during conventional intravesical instillation and during Synergo treatment.

b. Animal Studies

The purpose of the animal study was to administer a Synergo device treatment in an animal bladder, simulating actual clinical conditions and methods utilized in treating patients with the device. The aim was to demonstrate that during normal treatment conditions there are no risks of damage to the bladder or adjacent organs. This was achieved by temperature mapping of the bladder walls and adjacent organs during treatment with Synergo device and subsequent pathological evaluation of the organs after the treatment, in comparison with control subjects. Four adult sheep were used for this study; two were treated with the Synergo device for temperature mapping and pathological evaluation and two served as control models for the pathological evaluation.

Thermocouple junctions were sewn to the internal and external bladder surfaces as well as on neighboring organs. During the Synergo treatment session, thermocouple temperatures were monitored using a stand-alone, multi-channel temperature measuring system and thermocouple verification was performed. Temperature measurements were taken over the 60-minute treatment session, every 20 seconds. At extreme bladder temperatures of 46°C (normal temperature is $42 \pm 2^{\circ}\text{C}$), the maximum external wall temperature was [redacted] and the maximum adjacent organ temperature was [redacted] both well below the temperature to produce tissue damage.

The sheep were sacrificed and the harvested organs were macroscopically and histologically examined. Macroscopically, all organs of the four sheep were found to be intact. The main histological observation was ulceration of the epithelium, mild edema and inflammation of the lamina propria, as well as foci of fresh hemorrhage in the serosa. There was one microscopic focus of necrotic epithelium. These observations were noted at the suturing sites of the thermocouples to the organs and therefore, attributed to the surgical procedure and not to the Synergo treatment.

Temperature mapping of the urinary bladder and adjacent organs, and their pathological evaluation, clearly show that treatment with the Synergo System can be administered safely. There were no risks of irreversible damage to the urinary bladder or adjacent tissues even under “worse-case” conditions, such as high temperatures and anesthesia.

IX. Summary of Clinical Studies

The Synergo device has been used and studied in several clinical pre- and post-marketing studies since 1992. The device is legally marketed and is in routine commercial use in Europe and Israel since 2000. The following information summarizes each of the clinical studies submitted to the FDA in support of the PMA No. P010045. Together these studies show the efficacy of Synergo treatments in 260 patients, and the safety profile of 4502 treatment sessions in 507 patients.

1.1 Study 101.1

Study 101.1 is the pivotal study submitted in support of PMA No. P010045. It is a randomized, controlled trial designed to compare the efficacy and safety of the combined Synergo hyperthermia and Mitomycin-C treatment (hereinafter referred to as “Synergo treatment” or “Synergo Group”) to that of Mitomycin-C alone (hereinafter referred to as “MMC treatment” or “MMC Group”) in the treatment of STCCB, for the prevention of tumor recurrence after complete tumor eradication by transurethral resection (TUR). A total of 83 intermediate and high risk patients were recruited to the study; 42 randomized to Synergo treatment and 41 randomized to MMC treatment. Each Synergo treatment session included two 30 minutes cycles of intra-vesical hyperthermia in conjunction with intravesical instillation of 20 mg of MMC dissolved in 50 ml of distilled water. The MMC treatment included intravesical chemotherapy only, with the same doses of MMC. Both study group patients received 8 weekly inductive treatment sessions, followed by 4 monthly maintenance treatment sessions. Follow-up exams (cystoscopy and cytology) were performed every 3 months, up to 2 years follow-up. Primary efficacy endpoint was disease free survival at 2 years (comparison of recurrence rates) between the study groups.

The primary efficacy analysis results demonstrated that the Synergo treatment was significantly superior to MMC treatment. Kaplan-Meier estimated 2-year recurrence rates are presented in **Table 1** for the different patient cohorts.

Table 1 – Kaplan-Meier estimated 2 year recurrence rate, Study 101.1

Patient Population	MMC	Synergo	Log-Rank P
Evaluable: Randomized As Intended	54.4% (n=41)	25.0% (n=36)	0.0097
Evaluable: Randomized As Treated	61.6% (n=40)	18.9% (n=37)	0.0002
Per-Protocol	61.6% (n=40)	17.1% (n=35)	0.0002

The primary efficacy analysis was based on 77 evaluable patients who had at least one follow-up evaluation of recurrence status. Evaluable Patients: Randomized As intended, refers to the patient cohort in which the patients are grouped according to the treatment to which they should have been randomized according to the randomization scheme prepared by the study statistician. Evaluable Patients: Randomized As Treated, refers to the patient cohort in which the patients are grouped according to the treatment that they actually received during the study. The difference in patient cohorts were due to administrative errors, which occurred at the central randomization office resulting in 5

pairs of switched treatments. As can be seen from the results, the error had no effect on treatment outcome. The Per Protocol Patients refers to the patient cohort who did not have a major protocol deviation. As shown in **Table 1**, the rate of tumor recurrence is consistently lower and statistically significant in the Synergo group than in the MMC group regardless of the analysis populations used.

No tumor progression, no occurrence of CIS or urothelial call carcinoma, and no occurrence of distant metastasis were observed in the Synergo group. Furthermore, the cystectomy rate was lower in the Synergo group.

The safety analysis demonstrates that most of the expected adverse events were common amongst both treatment groups (**Table 2**). The only adverse events that presented significant difference between the treatment groups were pain and posterior wall tissue reaction, which were higher in patients treated with Synergo treatment than in patients treated with MMC treatment. These findings are anticipated due to the nature of the hyperthermia device. All these events were localized, transient and resolved without any significant residual effects and were asymptomatic.

No serious adverse events were classified by the investigators as treatment related.

Table 2 – Expected Adverse Events (All Study Patients)*

Adverse Events	MMC N=41		Synergo N=42	
	N	%	N	%
Dysuria	4	9.8	10	23.8
Hematuria	2	4.9	3	7.1
Tissue Reaction	20	48.8	21	50
Urethral Stenosis	2	4.9	3	7.1
Skin Allergy	2	4.9	5	11.9
Pain	-	-	17	40.5
Posterior Wall Tissue Reaction	1	2.4	27	64.3
Urinary Tract Infection	-	-	3	7.1
Bladder Wall Necrosis	2	4.9	2	4.8

*Based on Evaluable Patients: Randomized As Treated cohort

1.2 Study 102.1

Study 102.1 is an ongoing multi-center, multinational, randomized, controlled trial, designed to compare the efficacy and safety of the Synergo treatment to that of Bacillus Calmette-Guérin (BCG), in the treatment of STCCB for the prevention of tumor recurrence after complete tumor eradication by TUR. Although the study is planned for 300 patients, interim results are presented to FDA to support the results of the PMA pivotal study 101.1. The purpose of submitting the results of this study is not to conclusively evaluate the endpoints of this study. Rather, the purpose of submitting the results of this study is to demonstrate the consistency of the safety and efficacy results for

the Synergo treatment in another randomized, controlled, clinical study. At data lock 104 intermediate and high-risk patients were recruited, 51 were randomized to Synergo treatment and 53 to BCG treatment.

The general design of Study 102.1 and the pivotal Study 101.1 were similar except for the control arm, including similar treatment regimens, follow-up exams (cystoscopy and cytology) performed every 3 months, up to 2 year follow-up, and study endpoints. The primary efficacy endpoint was recurrence free survival at 2 years (comparison of recurrence rates) between the study groups.

The interim efficacy results are presented in **Table 3**. The recurrence rate in the Synergo group is substantially lower compared to the BCG group and is consistent with the findings in Study 101.1.

Table 3 – Study 102.1 interim results – Kaplan-Meier estimated 2 year recurrence rates (Per Protocol patient population)

Per Protocol Patient Population	BCG (n=48)	Synergo (n=42)
K-M Estimated 2-year Recurrence Rates	31.7%	16.9%

The adverse events reported for the Synergo patient population in Study 102.1 are mostly the same as those reported in the pivotal Study 101.1, including dysuria, hematuria, tissue reaction, urinary tract infection, pain, posterior wall tissue reaction and bladder wall necrosis. The most common adverse events are pain and posterior wall tissue reaction in both Study 101.1 and Study 102.1. When compared to the BCG group, systemic symptoms (arthralgia, fever, and fatigue) and urinary incontinence were significantly more frequent in the BCG group than in the Synergo group.

The interim results of Study 102.1 provide additional supportive evidence that Synergo is a safe and effective treatment for intermediate to high risk STCCB patients. Efficacy and safety data from this study are similar to those of the pivotal Study 101.1.

1.3 Synergo Arm Results (Studies 101.1 and 102.1)

Efficacy results from Synergo arms of Studies 101.1 and 102.1 were combined to provide additional supportive data. Study results demonstrated that the two Synergo arms were similar and therefore, may be pooled and analyzed as a single group. The pooled Synergo arms were compared to: (1) the MMC arm from Study 101.1, and (2) the BCG arm from Study 102.1.

The recurrence rates in the MMC arm and the BCG arm are significantly higher than that in the combined Synergo arms. The estimated 2-year recurrence rates are 17.1% for Synergo (combined studies 101.1 and 102.1), 31.7% for BCG, and 61.6% for MMC. The hazard ratio for MMC versus Synergo is 5.1 (95% confidence interval (CI)=2.5-10.3) and the hazard ratio for BCG versus Synergo is 2.3 (95% CI=1.1-5.0).

The combined analysis of Synergo arms of Studies 101.1 and 102.1 provides additional supportive evidence that the Synergo treatment is significantly more efficacious than MMC treatment and BCG treatment.

1.4 Comparison of Synergo Treatment with Historical MMC & BCG Controls

A systematic review of the efficacy of MMC and BCG treatment of STCCB was performed based on reports available in the literature to provide additional comparative data for the efficacy of Synergo treatment. The weighted estimates of 2-year recurrence rates for MMC and BCG treatments were calculated based on a meta-analysis of recurrence data extracted from the literature.

The 2-year recurrence rates for the Synergo group from Study 101.1 (18.9%), Study 102.1 (16.9%), and the combined Synergo arms (Studies 101.1 and 102.1) (17.1%) are significantly lower than the 2-year recurrence rates for either the MMC or BCG group observed in Study 101.1 (61.6%), Study 102.1 (31.7%), or reported in the literature (MMC 41.5%; BCG 35.6%).

1.5 European Prophylactic Patients (EPP)

Safety and efficacy data were collected from patients treated commercially in Europe and Israel with Synergo for prophylactic treatment of STCCB. Patients receiving Synergo treatment in these countries were selected for treatment, underwent treatment sessions and follow-up examinations in a similar manner to the Study 101.1 and Study 102.1 procedures.

A total of 186 intermediate and high-risk patients were commercially treated with Synergo treatment. As this experience is ongoing, many patients have not yet reached the first cystoscopy evaluation. The efficacy results of 122 evaluable patients presented a Kaplan-Meier estimated recurrence rate at 2 years of 32.2%. This result, which appears to be slightly less favorable than the results presented for Study 101.1 and Study 102.1, was influenced by several factors, including a higher risk patient population (higher median age, higher proportion of patients who failed on previous treatments, and a higher average number of previous tumor episodes) and treatments that were many times compromised by reimbursement issues causing inherent bias. That is, tumor free patients tend to have their follow-up in the primary care clinic (where the data is unavailable to the sponsor), as opposed to recurrent patients who are sent back to the hospital for treatment.

Despite the higher risk nature of these patients and the inherent bias described above, the EPP results are comparable to or better than or at least as good as the conventional, alternative treatments, including BCG and MMC. That is, the EPP estimated 2-year recurrence rate of 32.2% is far better than conventional MMC treatment reported for the Study 101.1 control arm for intermediate/high risk patients (62.6%) or reported in the literature for the general STCCB patient population (41.5%). Furthermore, the EPP

results are at least as good as the conventional BCG treatment reported for the Study 102.1 control arm (31.7%) or reported in the literature (35.6%).

More important than the efficacy results, the EPP provides additional safety data for another 186 patients treated with Synergo. The adverse events in the EPP were very similar to those presented for Study 101.1 and Study 102.1.

1.6 Additional Safety Data

Additional safety data in support of the Synergo treatment are provided for another 228 patients from the following studies or patient populations: (1) Bladder Salvage (BS) patients (n=82) treated with Synergo as a last resort treatment, after failed BCG treatments; (2) Study 101.4 patients (n=42) treated with Synergo for ablative (neo-adjuvant) treatment of bladder tumors in a controlled study originally submitted and then withdrawn from the PMA; and (3) European Ablation Patients (EAP) (n=104) also treated with Synergo for ablative (neo-adjuvant) treatment of bladder tumors in routine, commercial use of the device in Europe and Israel.

The safety results of these patients demonstrated that the adverse events were consistent with those presented for Study 101.1 and Study 102.1.

1.7 Conclusions

1.7.1 Efficacy

The Synergo PMA No. P010045 presents the efficacy results of 201 patients, including 79 patients from controlled, randomized studies and another 122 patients from real-life, commercial use of the device. The efficacy results are consistent throughout the studies and patient populations. The Synergo results are better than the conventional MMC and at least as good as if not better than BCG treatment results reported in the control arms of these studies or reported in the published literature or presented to FDA in the BCG NDA approval studies for the same intermediate/high risk patient populations, as shown in the **Table 4**.

Table 4 – Summary of Efficacy Results – Kaplan-Meier estimated 2-year recurrence rates

	Synergo	MMC	BCG
Study 101.1*	18.9%	61.6%	
Study 102.1	16.9%	--	31.7%
Combined Studies 101.1 + 102.1	17.1%	--	--
EPP	32.2%	--	--
Meta-Analysis of Literature Reports	--	41.5%	35.6%
BCG NDA (92-0306)	--	55%	43%

*Based on Evaluable Patients: Randomized As Treated cohort.

1.7.2 Safety

The safety profile of the Synergo treatment is very similar to that of routine intravesical use of chemotherapeutic agents, such as MMC and immunotherapy, such as BCG. The only anticipated adverse events that reported more frequently in the Synergo group were pain and posterior wall tissue reaction. In all occurrences of pain, the event was localized and transient during delivery of therapeutic heat during treatment and resolved without any residual effects. The higher incidence of posterior wall tissue reaction in the patients treated with the Synergo device was also anticipated due to the nature of the hyperthermia treatment. This event occurred due to the location of the RF antenna in the bladder, and in some cases there is an accumulative effect of the dissipated heat in the area around the antenna causing a small, localized area of superficial tissue reaction (hyperemia, inflammation, ulceration or eschar) in the posterior wall of the bladder. In fact, as MMC has been reported to also cause some necrotic reaction as a result of treatment, the combination of hyperthermia and MMC may have caused this reaction. In all Synergo patients, these events were noted during follow-up cystoscopies, superficial (no muscle involvement), asymptomatic and resolved without medical intervention or significant residual effects other than residual signs of hyperemia in a few patients.

Complications observed in the Synergo studies have been well reported with chemotherapy and/or immunotherapy intravesical instillations in the published literature. The most frequently observed immediate symptoms are irritative lower urinary tract problems, including dysuria, frequency/nocturia, urgency, pain and cramping and passing of debris in the urine, including blood or clots. Patients also experience bacterial cystitis, urinary incontinence and bladder perforation. Intravesical instillation of MMC in patients who have undergone resection of superficial bladder tumors had led to the development of indolent asymptomatic ulcers at the resection site which may persist for months before healing. Severe eczematous symptoms in patients receiving intravesical MMC appear to be due to delayed hypersensitivity reaction, which also appears to be responsible for the bladder irritation and cystitis which follow intravesical MMC. Furthermore, intravesical chemotherapy administration has led to severe bladder contracture.

In summary, the safety profile of the Synergo treatment is not substantially different from that of the conventionally available MMC or BCG treatments. The same types of side effects and adverse events have been reported and with similar frequencies. This has been seen in the Study 101.1 MMC Control group and the Study 102.1 BCG Control group, as well as in the published literature. Furthermore, systemic (and potentially life threatening) treatment related events seen with BCG have not been reported with the Synergo treatment.

The benefits offered by the Synergo treatment, as demonstrated by the clinical efficacy results, outweigh the risks of potential complications. This safety profile should be considered acceptable for a cancer treatment that has shown to be highly efficacious as demonstrated in the pivotal Study 101.1 and the additional supportive data.

The Synergo study data described in this PMA demonstrate that Synergo is a safe and effective prophylactic treatment for superficial transitional carcinoma of the bladder.

X. Panel Recommendation

XI. CDRH Decision

XII. Approval Specifications