

GASTROENTEROLOGY & UROLOGY DEVICES PANEL

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MEL-Medical Enterprises Ltd. Synergo SB-TS 101.1 Hyperthermia Device

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PROPOSED LABELING

Contents:

- (1) Physician Instructions Guide
- (2) Patient Labeling
- (3) Mitomycin C Package Insert

(Please note: The clinical results in the Physician Instructions Guide and Patient Labeling have not been updated to reflect the data included in the panel pack but the remainder of the labeling is accurate)

SYNERGO and MITOMYCIN FOR INJECTION, USP

MEDICAL ENTERPRISES LTD

Physician Instructions Guide

Physician Instructions Guide Table of Contents

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Preface

This Guide provides physicians with a brief summary of the indications, contraindications, adverse events and serious adverse events. The User Manual for the Synergo and Mitomycin for Injection, USP contains full and complete information including safety and efficacy data and operational safety details. This Guide does not replace the need to read thoroughly the User Manual for the Synergo and Mitomycin for Injection, USP for a complete understanding of the safe operation.

Caution: Federal (US) law restricts the Synergo Kit to sale by or on the order of a physician

1. General Description

The Synergo System, hereafter referred to simply as the “System”, is a computer-embedded intravesical irrigation system combined with an energy-delivering unit. The System includes an RF generator that delivers radio-frequency energy at 915 MHz, thermocouples for measuring and feedback of bladder temperature, a drug circulating unit, and a microprocessor with application specific software. The user interface consists of a computer, touch screen monitor, and keyboard. The irrigation system consists of a disposable-catheter tubing line set. The energy-delivering unit consists of a radio frequency (RF) generator and an antenna.

The treatment employs intravesical instillations of cooled Mitomycin for Injection, USP, concomitant with hyperthermia of the bladder wall induced by the emission of RF energy and monitored by thermocouples. A combination of hardware and software regulates the operation and presents the processed data on the monitor screen. The object of treatment is to heat the bladder wall while instilling the drug solution. The drug solution is cooled outside the body by the heat exchanger and continuously circulated in a closed circuit.

Application specific software monitors and records treatment parameters during a treatment session and provides a user interface that instantly alerts the operator if any parameters are out-of-range. For parameter deviations, the system is capable of automatically shutting down the RF heating.

A sterile, triple lumen, silicone, transurethral Foley type catheter is used for drug intravesical instillation. It is loaded with thermocouples to monitor bladder wall temperature and an RF antenna that radiates the bladder walls, heating them to the desired temperature. Two additional thermocouples on the feeding (RF) cable are used to monitor the temperature of the cable before the antenna (the hottest area of the table). An inflatable balloon anchors the catheter to the bladder neck.

The tubing line is connected to two lumens of the catheter. Liquid is pumped out from one lumen and instilled back, after being cooled, through another. A peristaltic pump keeps the inflow and outflow equal.

1.1. Catheter-Tubing Line Set

1.1.1. The Tubing Line Set

The tubing line set, together with the catheter system and the drug circulating unit, provides closed circuit circulation of the drug. The tubing line consists of a drug reservoir, Luer connectors, protection caps, three-way valves, unidirectional hydrophobic transducer protectors, particulate filter and clamps.

The section of the tubing line that leads from the bladder to the drug circulating unit has red colored components. The section of the line that delivers the cooled drug solution from the drug circulating unit to the bladder has blue colored components.

1.1.2. The Catheter System

The catheter system includes the silicon triple lumen 20 Fr Foley type catheter loaded with thermocouples and the antenna device. The thermocouples and antenna are installed into the

catheter channels through a pair of adapters that have a T connection to Luer connectors for attaching the tubing line. The thermocouple device is used to measure the temperatures at the epithelium of the bladder.

The antenna, which is located at the end of the feeding cable, emits the RF energy.

1.2. Drug Component Description (Mitomycin for Injection, USP)

Mitomycin (also known as Mitomycin-C) is an antibiotic isolated from the broth of *Streptomyces caespitosus*. Mitomycin has been shown to have antitumor activity. The compound is heat stable, has a high melting point, and is freely soluble in organic solvents.

Mitomycin is a sterile dry mixture of Mitomycin and Mannitol, which, when reconstituted with Sterile Distilled Water, provides a solution for intravesical instillation. Each vial contains Mitomycin 20 mg and Mannitol 40 mg.

2. Indications

The Synergo delivers heat transurethrally by means of radio frequency (RF) energy to the urinary bladder walls for the treatment of superficial transitional cell carcinoma of the bladder (STCCB), concomitant with intravesical instillation of Mitomycin for Injection, USP.

Synergo and Mitomycin C 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 and Mitomycin C treatment is clinically indicated for STCCB patients of intermediate and high risk.

3. Contraindications

Use of Synergo is contraindicated in the following patients and conditions:

- Because the patient's ability to detect pain is an essential safety mechanism, 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).
- Because electromagnetic radiation from the Synergo antenna may interfere with the operation of an electronic device, Synergo treatment is contraindicated in patients with cardiac pacemakers.
- Patients with Ta, G1 single transitional tumors at first episode of disease and patients with tumor stage greater than T₁ are not appropriate candidates for this treatment.
- 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 should not receive Synergo therapy.

- See also Contraindications of Mitomycin for Injection (Mitomycin package insert).

4. Warnings

- Hyperthermia treatment can be safely and effectively administered only after careful placement of antenna and thermocouple devices as described in the User Manual and with alert monitoring of tissue temperatures during treatment.
- Hyperthermia treatment presents a potential safety hazard in patients whose pain response has been decreased because of disease, previous surgery, ionizing radiation therapy, chemotherapy, or general anesthesia.
- Electromagnetic energy from radio frequency antennae may interfere with the operation of cardiac pacemakers or other implanted electronic devices.
- Large thermal doses (a continued elevation of moderately high temperature or a short extreme elevation of temperature) in normal tissue may result in transient regions of thermal aseptic necrosis.
- See also Warnings of Mitomycin for Injection (Mitomycin package insert).

5. Precautions

5.1 General Precautions

- Federal law restricts the Synergo Kit to sale by or on the order of a physician.
- Adherence to the recommended procedures for antenna and thermocouple placement is necessary to minimize the possibility of excessive temperature in normal tissue or inadequate temperature in the tumor.
- Proper antenna placement as recommended is required to reduce the possibility of posterior wall thermal reaction from the subsequent delivery of heat.
- Aseptic techniques should be used for the placement of catheters to avoid localized infections.
- To ensure accurate temperature monitoring during treatment, thermocouple function must be properly verified.
- In patients with compromised pain response, monitor closely other physiological indicators of excessive heat delivery.
- Patients with metallic implants (e.g., joint prostheses) should also be closely monitored during treatment because such objects may become excessively (and preferentially) heated.
- See also Precautions (section 7.4)

5.2 Treatment Procedure Precautions

- For single use only. Do not re-sterilize or reuse the Synergo Kit. Note the expiration date on the product label.
- For more information see the User Manual.

6. Pharmacokinetics of Mitomycin C with Synergo

The pharmacokinetics of Mitomycin C as delivered by the Synergo into the urinary bladder has been determined in patients with superficial transitional cell carcinoma of the bladder (STCCB). After Synergo treatment consisting of hyperthermia (HT) associated with intravesical instillation of Mitomycin C (MMC), the systemic plasma absorption of the drug was measured.

The control group of patients (N=12) received a 60-minute treatment session with MMC consisting of two 30-minute cycles at a dosage of 20mg/50ml of sterile water (2x20mg MMC), with bladder at body temperature.

The study group (N=13) received a 60 minute hyperthermia treatment (HT) in conjunction with MMC treatment at the same dosage and duration as the control group).

Table 6-1: Pharmacokinetic Results – Plasma concentration of MMC

| Time | Control Group 2x20 mg MMC alone | Test Group 2x20 mg MMC + Hyperthermia |
|---------|------------------------------------|--|
| 15 Min. | 2.52 ± 3.81 | 4.57 ± 3.82 |
| 30 Min. | 2.24 ± 3.20 | 5.23 ± 3.43 |
| 45 Min. | 2.64 ± 3.61 | 7.65 ± 6.24 |
| 60 Min. | 1.85 ± 3.14 | 7.57 ± 5.30 |

Maximum absorption was evident in both groups between 45 – 60 minutes after instillation of MMC with a significantly higher area under the curve in plasma (AUC_{plasma}) when HT was applied with MMC treatment, (187 (167 – 468) vs. 60 (33.8 – 108.8) ng*ml/min, p < 0.05).

The highest MMC plasma concentration reported in the study group was well below the critical toxic systemic level reported during intravenous administration of MMC. These findings support the safety of the treatment and demonstrate the effect on bladder wall permeability, resulting in enhanced MMC tissue penetration.

7. Drug Information (following intravenous injection of Mitomycin for Injection, USP)

7.1. Mechanism of Action

Mitomycin selectively inhibits the synthesis of deoxyribonucleic acid (DNA). The guanine and cytosine content correlates with the degree of Mitomycin-induced cross-linking. At high concentrations of the drug, cellular RNA and protein synthesis are also suppressed.

7.2. Contraindications

Mitomycin is contraindicated in patients who have demonstrated a hypersensitive or idiosyncratic reaction to it in the past.

Mitomycin is contraindicated in patients with thrombocytopenia, coagulation disorder, or an increase in bleeding tendency due to other causes.

7.3. Warnings

Patients being treated with Mitomycin must be observed carefully and frequently during and after therapy.

The use of Mitomycin results in a high incidence of bone marrow suppression, particularly thrombocytopenia and leukopenia. Therefore, the following studies should be obtained repeatedly during therapy and for at least 8 weeks following therapy: platelet count, white blood cell count, differential, and hemoglobin. The occurrence of a platelet count below 100,000/mm³ or a WBC below 4,000/mm³ or a progressive decline in either is an indication to withhold further therapy until blood counts have recovered above these levels.

Patients should be advised of the potential toxicity of this drug, particularly bone marrow suppression.

Deaths have been reported due to septicemia as a result of leukopenia due to the drug.

Patients receiving Mitomycin should be observed for evidence of renal toxicity. Mitomycin should not be given to patients with a serum creatinine greater than 1.7 mg percent.

Usage in Pregnancy: Safe use of Mitomycin in pregnant women has not been established.

Teratological changes have been noted in animal studies. The effect of Mitomycin on fertility is unknown.

7.4. Precautions

Acute shortness of breath and severe bronchospasm has been reported following the administration of Vinca alkaloids in patients who had previously or simultaneously received Mitomycin. The onset of this acute respiratory distress occurred within minutes to hours after the Vinca alkaloid injection. The total number of doses for each drug has varied considerably. Bronchodilators, steroids, and/or oxygen have produced symptomatic relief.

A few cases of adult respiratory distress syndrome have been reported in patients receiving Mitomycin in combination with other chemotherapy and maintained at FIO₂ concentrations greater than 50% perioperatively. Therefore, caution should be exercised using only enough oxygen to provide adequate arterial saturation since oxygen itself is toxic to the lungs. Careful attention should be paid to fluid balance and over- hydration should be avoided.

Bladder fibrosis/contraction has been reported with intravesical administration, which in rare cases has required cystectomy.

Nursing Mothers: It is not known if Mitomycin is found in human milk. Because many drugs are found in milk, it is recommended that women receiving Mitomycin not breast feed because of the potential for serious adverse reactions to the nursing infant from Mitomycin.

Pediatric Use: Safety and efficacy in pediatric patients have not been established.

7.5. Pharmacokinetics

In humans, Mitomycin is rapidly cleared from the serum after intravenous administration. Time required to reduce the serum concentration by 50% after a 30 mg bolus injection is 17 minutes. After injection of 30 mg, 20 mg, or 10 mg IV, the maximal serum concentrations were 2.4 µg/mL, 1.7 µg/mL, and 0.52 µg/mL, respectively. Clearance is affected primarily by metabolism in the liver, but metabolism occurs in other tissues as well. The rate of clearance is inversely proportional to the maximal serum concentration. It has been postulated that this relationship is due to saturation of the degradative pathways.

Approximately 10% of a dose of Mitomycin is excreted unchanged in the urine. Since metabolic pathways are saturated at relatively low doses, the percent of a dose excreted in urine increases with higher dosage. In children, excretion of intravenously administered Mitomycin is similar.

7.6. Animal Toxicology

Mitomycin has been found to be carcinogenic in rats and mice. At doses approximating the recommended clinical dose in humans, it produces a greater than 100% increase in tumor incidence in male Sprague-Dawley rats, and a greater than 50% increase in tumor incidence in female Swiss mice.

8. Adverse Events

8.1. Observed Expected and Unexpected Adverse Events during Intravesical Mitomycin Administration

Observed expected and unexpected adverse events experience comes from a clinical trial. See section 9 – Clinical Studies for a more complete description of the study design and results.

The total number of adverse events is more than the total number of patients in the study because some patients reported more than one adverse event.

Table 8-1: Principal Expected and Unexpected Adverse Events Observed in Clinical Study 101.1 (Number of patients)

| Adverse Events | | Treatment group (42) | Control group (41) |
|-----------------------------------|---------------------------------|----------------------|--------------------|
| Expected Adverse Events | | | |
| | Tissue Reaction | 50.0% (21) | 48.8% (20) |
| | Pain | 40.5% (17) | 0% |
| | Dysuria | 23.8% (10) | 9.8% (4) |
| | Hematuria | 7.1% (3) | 4.9% (2) |
| | Urethral Stenosis | 7.1% (3) | 4.9% (2) |
| | Posterior Wall Thermal Reaction | 64.3% (27) | 2.4% (1) |
| | MMC Skin Allergy | 11.9% (5) | 4.9% (2) |
| | Bladder Wall Necrosis | 4.8% (2) | 4.9% (2) |
| | Urinary Tract Infection | 7.1% (3) | |
| | Reduced Bladder Capacity | 4.7% (2) | |
| | False Passage | 2.4% (1) | |
| | | | |
| Unexpected Adverse Events | | | |
| | Hypotonic Bladder | 2.4% (1) | |
| | Anxiety | 2.4% (1) | |
| | Amnesia | 2.4% (1) | |
| | Fever + Urgency | | 2.4% (1) |
| | Weakness | | 2.4% (1) |
| | | | |
| Unexpected Serious Adverse Events | | | |
| | Hydronephrosis | | 2.4% (1) |
| | Nephrolithiasis | 2.4% (1) | |
| | Suspected Myocardial Infarction | 2.4% (1) | |
| | Bronchial Bleeding | 2.4% (1) | |

Analyzing the safety data demonstrates that Synergo hyperthermia in conjunction with Mitomycin C treatment does not cause major adverse events, other than what could be expected from urinary bladder catheterization, hyperthermia, and chemotherapy treatment.

8.2. Potential Adverse Events related to Mitomycin (Following IV injections)

Adverse events that may be associated with IV-injected Mitomycin C:

Arranged in the order of their incidence:

- Bone Marrow Toxicity
- Integument and Mucous Membrane Toxicity
- Renal Toxicity
- Pulmonary Toxicity
- Hemolytic Uremic Syndrome (HUS)
- Cardiac Toxicity (CHF – commonly associated with prior doxorubicin therapy)

Acute adverse events:

- Fever
- Anorexia
- Nausea
- Vomiting
- Acute Shortness of Breath / Severe Bronchospasm (following co-administration of vinca alkaloids)

Other (not unequivocally drug-related):

- Headache
- Blurring of Vision
- Confusion
- Drowsiness
- Syncope
- Fatigue
- Edema
- Thrombophlebitis
- Hematemesis
- Diarrhea
- Pain
- Malaise
- Asthenia

9. Clinical Studies

The principal evidence for the safety and efficacy of the Synergo came from a clinical study, the prophylactic study 101.1. The study evaluated the performance of Synergo treatment in patients with superficial transitional cell carcinoma of the bladder. Major study characteristics are summarized below.

Purpose: The purpose of this randomized study was to compare the effects of intravesical instillation of the chemotherapeutic agent Mitomycin C with and without hyperthermia as prophylactic treatment of transitional cell carcinoma of the bladder in intermediate and high risk patients. The principal endpoint of the study was follow-up of at least 24 month or up to first recurrence.

Design: The randomization procedure enrolled each patient into a study group or a control group, with the following treatment parameters:

- *Study group:* Local Hyperthermia in conjunction with intravesical instillation of MMC consisting of 2 x 20 mg MMC dissolved in 50 ml of sterile distilled water delivered in two portions of 30 minute treatments.
- *Control group:* Intravesical instillation of MMC alone with dosage and duration identical to that of the study group.

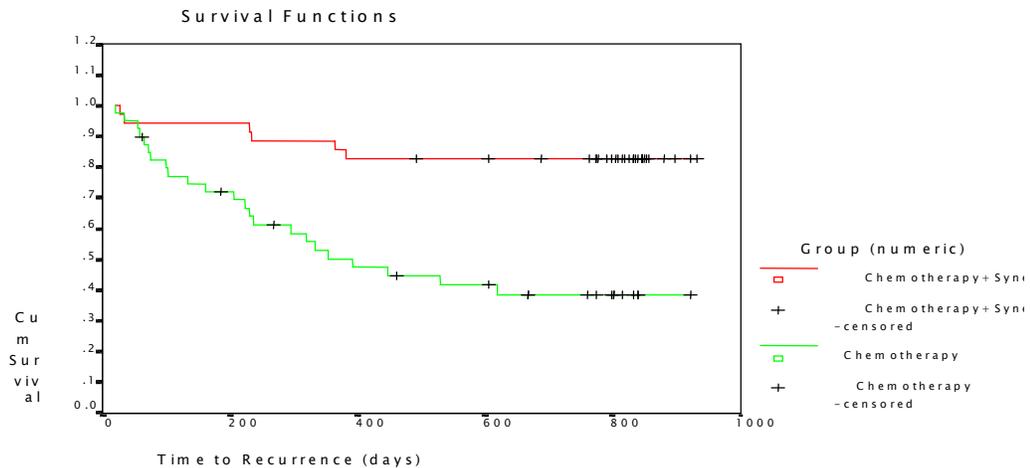
Methods: Both groups received eight (8) weekly inductive sessions, followed by four (4) monthly maintenance sessions. Each treatment session lasted 60 minutes. The treatment began within 20-40 days after eradication of tumors. Follow-up was performed at intervals of three months, until 24 months had elapsed or until the first recurrence, whichever came first.

Eligibility and Demographics: Male (83%) and female (17%) patients with Stage Ta or T1 and Grade G1-G3 STCCB following complete tumor eradication were enrolled in the study. Subjects with Ta, G1 single transitional tumors at first episode of disease were excluded from the study, as were patients with tumor stage > T1.

A total of eighty-three (83) patients were enrolled in the study at three clinical centers:

- Thirty-six (36) patients were enrolled in San Raffaele Hospital (Milan, Italy)
- Fourteen (14) patients were enrolled in University Hospital of Palermo (Palermo, Italy)
- Thirty-three (33) patients were enrolled in Rabin Medical Center - Beilinson Campus Hospital (Petah Tikva, Israel) between 1994 and January 1999.

Results: The following table presents survival analysis results for the per protocol cohort (n=75), up to 24 months follow-up, using Kaplan-Meier Recurrence-Free Survival Analysis with the log rank test for significance:



Tumor recurrence in the chemotherapy alone group is significantly sooner and more frequent. The results of this statistical test demonstrate that the difference in recurrence of tumors between the two treatment groups is highly significant ($P=0.0002$). There were no patients with progression in stage and only one (1) patient with a progression in grade (Mitomycin C alone group). There were no significant differences between the treatment groups regarding the incidence of distant metastasis.

Conclusion: In intermediate-high risk patients with superficial bladder cancer, the use of the Synergo system produced clinically significant results, namely the estimated probability of recurrence of STCCB at 2 year follow-up for the Synergo study arm (17%) is significantly lower ($P=0.002$) than the estimated probability of recurrence at 2 year follow-up for the Mitomycin C alone control arm (62%). The potential adverse events caused by the Synergo treatment (such as pain, dysuria and posterior wall necrosis) are known and previously reported in the literature with other similar devices and chemotherapy treatments (e.g., thiotepa, mitomycin C, adriamycin, and valrubicin alone).

10. Patient Counseling Information

Physicians should discuss the following topics when counseling patients about the Synergo treatment:

- Risks associated with the Synergo treatment
- Risks associated with Mitomycin drug for intravesical use
- Risks and benefits for this particular patient
- Disease and self-care measures before and after each treatment

11. How Supplied

Contents:

1. The catheter-tubing line set
2. Two (2) vials of 20 mg Mitomycin for Injection, USP (Bedford Laboratories™)

Sterile: The catheter system and tubing line set, each one separately packaged in a pouch, and both pouches further packaged in an additional pouch, are sterilized with ethylene oxide (EtO). Do not use if the package is opened or damaged. For one-time use only. Do not re-sterilize.

Storage:

Unreconstituted: The Synergo Kit is stored at controlled room temperature, 15° to 30°C (59° to 86°F). Mitomycin should be stored protected from light.

Reconstituted: with Sterile Distilled Water to a concentration of 0.4 mg per ml, Mitomycin is stable for 14 day refrigerated, 2° to 8° (36° to 46°F) or 7 days at room temperature. Protect the reconstituted solution from light.

12. User Manual

For the safe operation of the Synergo, read the User Manual.

12.1. Drug Dosage and Preparation

Each vial contains Mitomycin 20mg. To administer, add 50 ml Sterile Distilled Water. Do **NOT** use any other solution. Shake to dissolve and allow to stand at room temperature until a clear colored solution is obtained.

Each treatment session consists of two 30-minute cycles. For each cycle, use a fresh dose of 20 mg Mitomycin for Injection, USP, dissolved in 50 ml of Sterile Distilled Water.

For additional treatment steps, refer to the User Manual.

13. Patient Information

See the *Patient Information Guide*.

14. Patents

For the Synergo Device and its catheter-tubing line set: RE 37315 (issued in the United States) and EP: 612228 (issued in France, Great Britain, and the Netherlands). Mitomycin is a generic drug and all marketing exclusivity and patents have expired (source FDA Orange Book).

15. Disclaimer of Warranty and Limitation of Remedy

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