SUMMARY FOR BASIS OF APPROVAL

REFERENCE NUMBER: 92-0306

TRADE NAME: TICE® BCG

GENERIC NAME: BCG LIVE

MANUFACTURER: Organon Teknika Corporation
100 Akzo Avenue
Durham, NC 27112

DATE OF APPROVAL: August 4, 1998

INDICATIONS AND USAGE

Intravesical Use for Carcinoma In Situ of the Bladder. Intravesical instillation of TICE® BCG is indicated for the treatment of carcinoma-in-situ of the bladder in the following circumstances:

1. The primary treatment of CIS of the bladder (after transurethial resection) either with or without associated papillary tumors.
2. The secondary treatment of CIS of the bladder in patients treated with other intravesical agents who have relapsed or failed to respond.
3. The primary or secondary treatment of CIS in patients who have contraindications to radical surgery.

Intravesical Use for TaT1 Carcinoma of the Bladder. The approval of this product license supplement extends the indication for intravesical instillation of TICE® BCG to the adjuvant treatment following transurethal resection of stage Ta or T1 papillary tumors of the bladder, which are at high risk of recurrence.

TICE® BCG is not indicated for patients with a low risk of recurrence or for the treatment of unresected papillary tumors. TICE® BCG is also not indicated for stage T2 or higher papillary tumors and for invasive cancer.

DOSAGE FORM, ROUTE OF ADMINISTRATION, AND RECOMMENDED DOSAGE

TICE® BCG is an attenuated live culture preparation of the Bacillus of Calmette and Guerin strain (BCG) of *Mycobacterium bovis*. The TICE strain was developed at the University of Illinois from a strain originated at the Pasteur Institute.

The medium in which the BCG organism is grown for the preparation of the freeze-dried cake is composed of the following: glycerin, asparagine, citric acid, potassium phosphate, magnesium sulfate, and iron ammonium citrate. The final preparation prior to freeze drying also contains lactose. No preservatives are added.

TICE® BCG is supplied as a freeze-dried powder in a box containing one vial. Each vial contains 1 to 8 x 10^8 colony forming units, which is essentially equivalent to 50 mg (wet weight). The dose for the intravesical treatment of CIS and for prophylaxis of recurrent papillary tumors consists of one vial of TICE® BCG suspended in 50 ml of preservative-free saline.

The TICE® BCG product should be reconstituted using aseptic technique. Since at least two cases of BCG meningitis have been attributed to nosocomial contamination of intrathecal methotrexate, parenteral drugs should not be prepared in the same area where BCG has been reconstituted. All equipment, supplies, and receptacles in contact with TICE® BCG should be considered biohazardous. The pharmacist or the individual responsible for mixing the BCG should wear gloves, mask and gown to avoid inadvertent exposure to broken skin or inhalation of BCG organisms.

To prepare the BCG suspension, one ml of sterile-preservative free saline (0.9% sodium chloride USP) is drawn into a small syringe and then added to one vial of TICE® BCG. After gentle mixing, the BCG suspension is dispensed from the syringe into either another syringe which contains 49 ml of saline diluent or into a 50 ml plastic i.v. saline bag. The suspended TICE® BCG should be used immediately after preparation and should be discarded after two hours.

TICE® BCG should be administered 7-14 days after bladder biopsy. Patients should not drink fluids for four hours before treatment and should empty their bladder prior to BCG administration. The reconstituted BCG is installed into the bladder by gravity flow using a catheter . TICE® BCG should be retained in the bladder for two hours and then voided. While the BCG is retained in the bladder, the patient should be repositioned from the left side to the right side and the back side to the abdomen every 15 minutes to maximize surface exposure to the agent.

A standard treatment schedule of TICE® BCG consists of one intravesicular instillation per week for six weeks. The schedule may be repeated once if tumor remission has not been achieved and the clinical circumstances warrant. Thereafter, BCG administration may be continued at monthly intervals for 6-12 months.

MANUFACTURING AND CONTROLS

A. Manufacturing and Controls

BCG originated at the Pasteur Institute from a virulent strain of *Mycobacterium bovis* that was attenuated by repeated transfer in the laboratory of Calmette and Guerin. The daughter strain that became TICE® BCG was obtained directly from the Pasteur Institute in 1934. Although this strain was maintained by continuous passage for more than 20 years, TICE® BCG is now stored as a ——— primary seed lot at ——.

Production is initiated by ———

——— After completion of the harvest, the vials are filled and the BCG is lyophilized. The vials are then stoppered and quarantined in storage containers pending completion of control testing. The assays required for release of final product include avirulence, potency (enumeration of CFUs by a serial dilution assay), particulate, and the potential to induce delayed-type hypersensitivity to tuberculin in guinea pigs.

B. Stability Studies

In December 1997, the approval of product license supplement 97-0088 included the change from an ampoule to a vial final configuration. The data submitted in supplement 97-0088 supported an eighteen month dating period for TICE® BCG supplied in vials and stored at 2-8 °C. As a result of the 97-0088 approval, Organon Teknika committed to a stabilty monitoring program and the annual submission of stability data.

C. Validation

In 1994, CBER approved PLA and ELA supplements relating to the transfer of Organon Teknika's BCG production from Chicago to Durham, North Carolina. During this process, all major equipment and processes used for the production of BCG were validated. Procedures were also established and validated for monitoring the environmental conditions of the manufacturing areas. These procedures have been examined as part of the ongoing reporting required for the licensed product.

D. Labeling

In conjunction with approval of this supplement, CBER requested that Organon Teknika market two BCG products - one indicated for the treatment of bladder cancer (TICE® BCG Live) and the other indicated for vaccination against tuberculosis (BCG Vaccine). The TICE® BCG Live bladder cancer labeling, including container and package labels and the package insert, were reviewed for compliance with the appropriate sections of 21 CFR and were found to be satisfactory.

E. Establishment Inspection

Inspections of the manufacturing and quality control facilities in March and April 1997 revealed particulate contamination of the BCG product. As a result of this inspection, a warning letter was issued. Organon Teknika's subsequent response to the warning letter was adequate. Modifications in the manufacturing process and the development of a validated particulate assay have reduced particulate contamination to acceptable levels. The particulate assay has been added as a test required for lot release.

F. Environmental Impact Analysis Report

This new indication involves no change in the manufacturing process or facilities. No adverse effects on the environment are expected from licensure of the product. An Environmental Assessment report was submitted by Organon Teknika on July 15, 1994 and a finding of no significant impact was accepted.

PHARMACOLOGY

Intravesical TICE® BCG has been used as a therapy for and prophylaxis against recurrent tumors in patients with carcinoma-in-situ of the urinary bladder and to prevent recurrence of stage TaT1 papillary tumors of the bladder which are at high risk of recurrence. The precise mechanism of action is unknown.

MEDICAL

A. Background

Carcinoma of the bladder accounts for about 2% of all solid tumors in the United States with more than 50,000 new cases being diagnosed each year. The peak prevalence of bladder cancer is in individuals 60-70 years old and several etiologic factors have been implicated including smoking and exposure to industrial chemicals.

Pathologically, carcinoma of the bladder is categorized by grade (usually I - IV) and by depth of malignancy (either superficial, invasive, or metastatic bladder cancer). Superficial bladder cancer, which is confined to the bladder epithelium, usually presents as papillary tumors (stages Ta or T1) or carcinoma-in-situ. Diagnosis of bladder cancer is by cytoscopy and biopsy. At the time of diagnosis, about 70% of patients have only superficial disease, 25% have locally invasive disease, and 5% already have distant metatasis.

Superficial bladder cancer is treated with transurethal resection (TURBT) and /or fulguration. Cytoscopy is usually reserved for those tumors which cannot be resected transurethally. After TURBT, 50% of patients remain disease free; however the other half will experience multiple recurrences with about 10% developing invasive or metastatic disease within 3-4 years. Superficial recurrences are treated with TURBT, often followed by intravesical chemotherapy to prevent or delay any additional recurrence. Patients who are considered at high risk for recurrence after the initial TURBT (e.g. high grade, multi-focal, and/or large tumors) , or those with concurrent CIS are frequently given intravesical adjunct therapy as prophylaxis against recurrence. Intravesical BCG administration is the treatment of choice for this adjunct therapy.

TICE® BCG was licensed in the United States in 1989 for the treatment of carcinoma-in-situ but not for papillary Ta or T1 lesions. To obtain licensure for the treatment of carcinoma-in-situ with the TICE substrain, the sponsor submitted efficacy data on 119 evaluable patients with biopsy proven CIS. The data was derived from six uncontrolled phase II trials. No controlled phase III trials were done. The primary endpoint evaluated was the incidence of complete responses (CR). The initial response based on a two year follow-up was 75.6%. After a median duration of follow-up of 47 months, there were 45 CRs, resulting in an overall long-term response of 38%. At this time, 85 patients (71%) were alive, 18 patients (15%) had died of bladder cancer and 13 (12%) had died of other causes. The advisory committee noted that historical data obtained prior to the use of intravesical BCG showed that 34% of CIS patients died of this disease in five years.

B. Studies of Safety and Efficacy for the Treatment of Papillary Tumors of the Bladder

Results from two randomized phase III trials of TICE® BCG and Mitomycin-C (MMC) were submitted in support of the labeling extension. The first study, "The comparative study or intravesical instillation of Mitomycin-C, BCG-RIVM, and TICE® BCG in pTa-pT1 papillary carcinoma and primary carcinoma-in-situ of the urinary bladder, " was sponsored by the Urology Trial Office, at the Nijmegen University Hospital, the Netherlands. The second study, " Randomized Prospective Comparison of Bacillus Calmette Guerin and Mitomycin-C Therapy and Prophylaxis in Superficial Transitional Cell Carcinoma of the Bladder ; A Phase III

Intergroup (SWOG 8795, ECOG 1868) Study" was sponsored by the Southwest Oncology Group (SWOG) in conjunction with the Eastern Cooperative Oncology Group (ECOG).

Both of these studies utilized MMC as the control. The use of MMC in patients with superficial bladder cancer is an off-label use. MMC is neither indicated for use in patients with bladder cancer, nor for administration by the intravesical route. There is no consensus on effective treatment schedules. Not all comparative trials of MMC vs. no further treatment following the transurethral resection of bladder tumor(s) have shown a significant effect for MMC. Data regarding the contribution of maintenance MMC have also been conflicting. MMC dosages studied have ranged from 20 mg to 60 mg in sterile water, usually instilled at a concentration of 1 mg/ml. Intravesical therapy is a form of topical therapy: drug concentration and exposure duration are important determinants of effect.

PIVOTAL TRIAL I - THE NIJMEGEN STUDY

a. General

The Nijmegen study was conducted by a total of 26 investigators, participating from 24 institutions. The study opened in April 1987 and closed in December 1990.

b. Study Design

The effectiveness of three treatments (TICE® BCG, BCG-RIVM, and MMC) was compared in patients with primary or recurrent stages CIS, Ta, or T1 cancer of the bladder. Patients could not have received chemotherapy, immunotherapy, or radiotherapy. All papillary tumors were to have been resected. A negative urinary cytology was required for study entry. The primary study endpoint, the disease-free interval, was defined as the time from TURBT to the first positive biopsy.

Patients were randomized to:

TICE® BCG - 5×10^8 CFU/50 ml per wk x 6 weeks,

-or-

BCG-RIVM - 5×10^8 CFU/50 ml per wk x 6 weeks,

-or-

MMC - 30 mg/50 ml per wk x 4, then per month x 5.

Therapy was initiated 7-15 days post-TURBT. Patients were cystoscoped at 3 and 6 months. Patients with recurrence and progression to stage $\geq$ T2 were dropped from the study. Patients with recurrence at 3 or 6 months but without progression to stage $\geq$T2 continued on study after a repeat TURBT; patients on the TICE® BCG arm received a second 6-week BCG course; and patients on the MMC arm continued on monthly MMC maintenance. Urinalysis and cytology were obtained at weeks 2, 4, and 6 for the BCG arms and with each MMC instillation. After 6 months, the three arms were monitored similarly with cytologies and cystoscopies every 3 months until recurrence. A positive cytology alone was not considered to be a recurrence. Tumor recurrence required biopsy confirmation.

Patients were taken off study for:

- Recurrences at both 3 and 6 months post-TURBT
- First recurrence at or after 9 months post-TURBT
- Tumor progression to stage $\geq$T2
- Toxicity
- Protocol violation
- Lost to follow-up
- Refusal of treatment
- Death

The study endpoints were:

- Disease-free interval
- Recurrence rate per 100 patient-months
- Progression to a higher stage and/or grade
- The incidence and severity of adverse reactions.

c. Nijmegen Study Results - Efficacy

Four hundred sixty-nine patients were accrued. Thirty-two patients were not evaluable: 17 were considered ineligible and 15 were withdrawn before treatment. Fifty patients had carcinoma-in-situ. Thus, there were 367 evaluable patients with non-CIS superficial bladder cancer: 117 in the TICE® BCG arm, 134 in the BCG-RIVM arm, and 136 in the MMC arm. A summary of the 469 patients is given in Table 1.

TABLE 1 - Disposition of Study Population

PATIENT DISPOSITION	STUDY ARM TICE® BCG N=154	BCG RIVM N=159	MMC N=156
Ineligible/not evaluable	14	10	8
Evaluable:	140	149	148
Carcinoma-in-situ	23	15	12
TaT1 papillary tumors	117	134	136

The arms were balanced. Twenty-eight patients (24%) in the TICE® BCG arm, 32 patients (24%) in the BCG-RIVM arm, and 24 patients (18%) in the MMC arm had low-grade (TaG1) tumors. The median duration of follow-up was 22 months (range 3-54 months).

Complete documentation of disease status (i. e., by cystoscopy, biopsy, and cytology) was obtained in 325 of the 367 patients (84%). A documented recurrence required a positive cystoscopy, a positive cytology, and a positive biopsy - a positive cytology per se was not classified as a recurrence. A breakdown of the study arms according to documentation of disease status is given in Table 2.

TABLE 2 - Nijmegen Study Documented Disease Status

DISEASE STATUS	STUDY ARM TICE® BCG N=117	BCG RIVM N=134	MMC N=136
Documented Recurrence	52 (44%)	46 (34%)	40 (29%)
Documented Disease-free	45 (38%)	66 (49%)	76 (56%)
No Cytology Performed	13 (11%)	11 (8%)	16 (12%)
Positive Cytology Only	2 (2%)	2 (1%)	2 (1%)
No data	5 (4%)	9 (7%)	2 (1%)

Fifty-two of the 117 patients (44%) on the TICE® BCG arm, 46 of the 134 patients (34%) on the BCG-RIVM arm, and 76 of the 136 patients (29%) on the MMC arm had documented disease recurrence. For the 371 patients with data, the hypothesis of no difference in the incidence of recurrence among the three arms was tested at a significance level $\alpha=0.05$ using the Pearson chi-squared statistic with two degrees of freedom. The observed chi-squared statistic was 7.2, with a p-value of 0.028. A subsequent

test comparing TICE® BCG to MMC was performed using a chi-squared statistic with two degrees of freedom. The observed statistic was 6.5, with a p-value of 0.039. On the Kaplan-Meier plot of the time-to-recurrence, the median disease-free interval in the TICE® BCG arm was 1028 days (2.8 years): the medians in the other two arms were not reached. The overall differences between the three arms were not significant by the log-rank test (p=0.08)

An intent-to-treat analysis was done using all 387 patients, placing the patients with unknown disease status in the no recurrence arm. A hypothesis test of no difference among the three arms was performed, and the null hypothesis was rejected with an observed chi-squared statistic of 6.4, and a p value of 0.042. The chi-squared test with two degrees of freedom comparing TICE® BCG to MMC yielded a value of 5.5, and a p-value of 0.064.

SUMMARY - These analyses of the Nijmegen data suggest that TICE® BCG has anti-tumor activity, although the activity of MMC is superior to TICE®BCG as defined in this trial. It must be noted, however, that the primary endpoint was time-to-recurrence, not incidence of recurrence. In fact, if patients in the MMC arm were not as closely followed as patients in the two BCG arms, or length of follow-up was markedly different among the arms, then the analysis comparing incidence of recurrence may not be valid. There is insufficient information in the database from which to speculate upon differential follow-up.

These various analyses of the data are suggestive of the superiority of MMC relative to intravesical BCG in this study. However, it should be emphasized that the BCG treatment arm of this study consisted of a single six week induction regimen. This treatment schedule is less extensive than the schedule used in SWOG study 8795.

d. Nijmegen Study Results - Safety

Adverse drug reaction (ADR) data were presented on all 437 evaluable patients, CIS and non-CIS. The ADRs reported are summarized in Table 3.

With the exception of allergic reactions which were much more common in the MMC arm (2% vs. 5%), side effects were more frequent and severe in the BCG arms. Statistically significant differences in drug-induced cystitis, "other local side effects", and systemic side effects were seen. Both BCG products caused more severe side effects than MMC : 21/140 patients (15%) on TICE® BCG and 19/149 patients (13%) on BCG-RIVM had treatment delayed or discontinued because of toxicity compared to 6/148 patients (4%) on MMC. There were no unexpected adverse reactions, nor were there any treatment-

related deaths. No data were presented on the number of patients who received antituberculous therapy in this study.

TABLE 3 - Nijmegen Study Adverse Reaction Data

	STUDY ARM		
ADVERSE REACTION	TICE® BCG N= 140	BCG-RIVM N= 149	MMC N=148
Drug-induced cystitis	42 (30%)	48 (32%)	26 (17%)
Bacterial cystitis	38 (27%)	35 (23%)	27 (18%)
Other local side effects	23 (16%)	22 (15%)	7 (5%)
Malaise	10 (7%)	5 (3%)	2 (1%)
Flu-like symptoms	11 (8%)	4 (3%)	1 (<1%)
Fever	9 (6%)	5 (3%)	0
Allergic symptoms	3 (2%)	3 (2%)	7 (5%)
Nausea	2 (1%)	1 (<1%)	0
Arthralgia	1 (<1%)	1 (<1%)	0
Sepsis	1 (<1%)	0	0
Pneumonitis	0	1 (<1%)	0
Rash	0	0	1 (<1%)
Systemic symptoms	4 (3%)	10 (7%)	2 (10%)

PIVOTAL TRIAL 2 - SWOG STUDY 8795.

a. General

The SWOG trial opened in December 1988 with 51 U. S. centers participating. The projected sample size was 720 patients; however, in December 1991 the statistical criteria were revised because of slow accrual. The revised sample size was 663 patients. Interim analyses were to have been performed after 55% and 84% of patients were entered. The first interim analysis was performed in March 1992 on 349 patients. It revealed the superiority of the TICE® BCG arm with respect to prolongation of time to first recurrence in patients without carcinoma-in-situ (p=0.001), and the trial was stopped in May 1992.

b. Study Design

SWOG 8795 was an open-label, prospective, and randomized trial which compared the efficacies of TICE® BCG and MMC, using the time to recurrence or progression as the primary endpoint. Patients had stage Ta or T1 transitional cell carcinoma of the bladder and were considered to be at high risk for recurrence, as defined by the presence of Ta lesions with $\geq$ 2 resections (including initial TURBT) within 56 weeks prior to registration; Ta lesions presenting with $\geq$ 3 papillary tumors within 16 weeks prior to registration; or T1 lesions presenting within 16 weeks prior to registration.

Concurrent CIS was allowed but CIS alone was not. Prior intravesical BCG, MMC, or systemic chemotherapy was not allowed. Resection of all papillary tumors (cystocopy confirmed) was required prior to study entry. Patients were stratified by the presence or absence of concurrent CIS and randomized to:

TICE® BCG - 5x 10^8 CFU/50 ml for wk 1-6, wk 8 & wk12, then monthly x 9,

-or-

MMC - 20 mg/20 ml for wk 1-6, wk 8 & wk12, then monthly x 9

Treatment was initiated 1-2 weeks post-TURBT. Cystoscopy and cytology were performed every 3 months for 2 years. Patients were removed from study for:

- Recurrence or progression
- Unacceptable toxicity
- Intercurrent illness
- Refusal of treatment or
- Death.

Patients were to be followed until death.

Toxicity was graded by the SWOG common toxicity criteria and a supplementary toxicity criteria scale, which was developed specifically for intravesical therapy with special attention to BCG toxicities. TICE® BCG was withheld for grade $\geq$2 local bladder toxicity or grade $\geq$3 systemic toxicity . Following resolution to grade 0, isoniazid (INH) was given and TICE® BCG was resumed at 50% of dose. TICE® BCG was discontinued and triple antituberculous therapy (INH, rifampin, and cycloserine) was begun for systemic BCG infections. MMC was withheld when a generalized rash was observed and restarted at full dose after resolution. MMC was permanently discontinued for bladder contraction.

c. SWOG Study 8795 Results - Efficacy

At the time of the interim analysis, 453 patients had been registered. An additional 16 patients were accrued prior to termination of the study, for a total of 469 patients. Of these patients, 22 were subsequently declared ineligible. Among the 447 eligible patients, 66 patients had concurrent CIS. Thus, 381 patients with non-CIS superficial bladder cancer received treatment on study. Four patients (three in the TICE® BCG arm and one in the MMC arm) were lost to follow-up, leaving 377 patients evaluable for analysis: 191 in the TICE® BCG arm and 186 in the MMC arm. A summary of the study population is given in Table 4.

TABLE 4 - Disposition of the Study Population of SWOG Study 3795

	STUDY ARM	
PATIENT DISPOSITION	TICE® BCG N=237	MMC N=232
Ineligible	12	10
Concurrent carcinoma-in-situ	31	35
TaT1 papillary tumors:	194	187
Not evaluable	3	1
Evaluable	191	186

The study population was balanced with respect to age, sex, and race. Tumor stage and grade were not listed in the most recent data set submitted. The hard copy line listings from the preliminary analysis (December 1992) included the tumor stage and grade for 312 patients. The tumor stage and grade were balanced in this data set. One hundred thirty-nine patients (45%) had TaG1 lesions - 64 (41%) in the TICE® BCG arm and 75 (49%) in the MMC arm.

Patient status at time of the last analysis is given in Table 5.

TABLE 5 - Status of SWOG Study 8795 Study Population at Last Analysis

	STUDY ARM	
STATUS OF PATIENT	TICE® BCG N=191	MMC N=186
Alive without recurrence	104	50
Alive with recurrence	62	78
Died without recurrence	10	5
Died with recurrence:	15	23
Due to cancer	8	12
Not due to cancer	6	10
Unknown	1	1

As seen in Table 5, 87/191 patients with only papillary tumors (46%) in the TICE® BCG arm died or recurred vs 106/186 patients (57%) in the MMC arm. When analyzed by SWOG, all deaths were considered to be treatment failures, regardless of cause of death. The primary efficacy endpoint was time to recurrence, which was defined as time to first recurrence, progression or death. The null hypothesis of no difference between recurrence times was tested using the log rank test. The resulting chi-squared statistic was 4.4, with a p-value of 0.016. The median time to recurrence or death was 44 months in the TICE® BCG arm and 22 months in the MMC arm. The relative risk (hazard ratio) was estimated to be 1.4.

SWOG also analyzed the time to progression or death. Patients with an event which could signify progression such as cystectomy, radiation therapy, or systemic chemotherapy were considered to have progressed. Thirty-two patients (17%) in the TICE® BCG arm and 36 patients (19%) in the MMC arm progressed or died. The median times to progression or death were not reached in either arm; a log-rank test of the null hypothesis of no difference on progression or death between the two arms was not significant (chi-squared statistic 0.5, p=0.46). All cause mortality was similarly analyzed. Twenty-five patients (13%) in the TICE® BCG arm and 28 patients (15%) in the MMC arm died. The median survival times could not be estimated from the data.

The outcome of each patient at 2 years was analyzed. Patients who had not recurred at 2 years were censored, and patients who recurred, progressed, or died within the 2 years were considered failures at the time of the event. Day 775 was arbitrarily chosen as the cut off point for 2 years. The result of this analysis is summarized in Table 6.

TABLE 6 - SWOG Study 8795 Study Results at 2 years

	STUDY ARM	
PATIENT STATUS	TICE® BCG N=191	MMC N=186
Recurred, progressed, or died	78	97
Alive without disease	113	89

An association between treatment and outcome was tested using a Pearson chi-square test. The chi-squared statistic was 4.4, with an associated p-value of 0.036. A log rank test was performed to test the null hypothesis of no difference in time to recurrence. The test statistic (chi-squared with 1 degree of freedom) was 4.9, with an associated p-value of 0.026. The median time to recurrence in the TICE® BCG arm was not reached. The median time to recurrence in the MMC arm was 22 months.

Of the 377 patients with follow-up data, 201 did not complete the 12-month course of treatment. Reasons for not completing treatment included relapse or progression of disease, refusing treatment, and excess toxicity. A conservative way to assess the benefit of treatment would be to count only patients who successfully completed treatment and experienced no relapse as treatment successes. This analysis is shown in Table 7.

TABLE 7 - SWOG Study 8795 Study Results

	AT END OF 2 YEAR STUDY		AT LONG TERM FOLLOW-UP	
PATIENT STATUS	TICE® BCG	MMC	TICE® BCG	MMC
Completed therapy & disease-free	82	60	74	53
Recurred/Did not complete therapy	109	126	117	133

The Pearson chi-squared tests of the association between treatment and outcome give p-values below 0.05, both at the end of the protocol specified 2-year study period (p=0.042) and with long-term follow-up (p=0.046).

An intent-to-treat analysis was performed on the 392 patients with resectable Ta/T1 tumors, regardless of their eligibility status. The breakdown of recurrence by treatment is shown in Table 8, using both the protocol-specified 2-year follow-up data and also the long-term follow-up data. These 2 year and long-term follow-up data indicate the superiority of TICE BCG therapy relative to MMC treatment.

TABLE 8 - SWOG Study 8795 Recurrence by Intent-to-Treat

PATIENT STATUS	AT END OF 2 YEAR STUDY TICE® BCG	AT END OF 2 YEAR STUDY MMC	AT LONG-TERM FOLLOW-UP TICE® BCG	AT LONG-TERM FOLLOW-UP MMC
Recurrence or death	80	101	89	110
Alive & disease--free	114	91	105	82
Unknown status	5	1	5	1

A series of Pearson chi-squared tests was performed to test the association between treatment and outcome, based both only on the protocol-specified 2-year follow-up data and also using the long-term follow-up data. In one set of analyses, all patients with unknown outcome were considered to be recurrences. In the other, patients in the TICE® BCG arm with unknown outcome were considered to be recurrences, while the subject in the MMC arm with an unknown outcome was considered a non-recurrence (worst-case scenario). The results of these analyses are given in Table 9.

TABLE 9 - SWOG Study 8795 Intent-to-Treat Analyses

	DATA SET USED FOR ANALYSIS			
	2-YEAR DATA		LONG-TERM DATA	
TYPE OF ANALYSIS	X^2	p-VALUE	X^2	p-VALUE
Unknown outcome	3.6	0.056	3.7	0.053
Worst-case scenario	3.3	0.071	3.4	0.067

The results of all these analyses are consistent with the earlier analyses which gave evidence of the superiority of the TICE® BCG arm.

SWOG study 8795 intended to treat patients at high risk of recurrence. The original eligibility criteria required eligible subjects to have at least two occurrences of tumor within 56 weeks of registration. The eligibility criteria were amended 9 months into the study to include subjects who presented with three or more tumors within 16 weeks of randomization. These patients may or may not have had previous tumor recurrences. It could not be established which of the patients were entered under the multiple occurrence criteria or the multiple tumor criteria. As noted previously almost one-half of the patients had TaG1 tumors at baseline. Two subset analyses were performed for the primary efficacy endpoint based on baseline tumor stage and grade. The first included only subjects with TaG1 tumors at baseline and the second included all other patients with baseline tumor stage and grade data. Neither analysis gave statistically

significant differences between the two treatment arms, although the trends pointed toward the superiority of the TICE® BCG , especially for the patients with non-TaG1 tumors. The results of these analyses are summarized in Table 10.

TABLE 10 - SWOG Study 8795 Results by Tumor Stage and Grade

	TaG1 TUMORS		NON-TaG1 TUMORS	
PARAMETER	TICE® BCG N=64	MMC N=75	TICE® BCG N=93	MMC N=78
Recurrence	29 (45%)	39 (52%)	48 (52%)	47 (60%)
No recurrence	35 (55%)	36 (48%)	45 (48%)	31 (40%)
Median time to recurrence (mo)	not reached	25	36	13

SUMMARY - SWOG study 8795 provides substantial evidence for the superiority of TICE® BCG over MMC in preventing the recurrence of Ta/T1 superficial bladder cancer. Analysis of the incidence of recurrence at 2 years showed a statistically significant advantage for TICE® BCG.

d. SWOG Study 8795 Results - Safety

Safety data on 442 patients were submitted. This data represented all patients (CIS and non-CIS) randomized, for whom follow-up data are available. The data were limited to include only those side effects occurring in ≥ 10% of patients. The study report stated "There were no treatment related deaths or grade 4 toxicities in either arm." A summary of the toxicity reported in SWOG study 8795 is given in Table 11.

TABLE 11 - SWOG study 8795 Adverse Reaction Data

	STUDY ARM			
	TICE® BCG (N=222)		MMC (N=220)	
ADVERSE REACTION	ALL GRADES	GRADE > 2	ALL GRADES	GRADE > 2
Dysuria	115 (52%)	6 (3%)	77 (35%)	5 (2%)
Urgency/frequency	112 (50%)	5 (2%)	63 (29%)	7 (3%)
Hematuria	85 (38%)	6 (3%)	56 (25%)	5 (2%)
Flu-like symptoms	54 (24%)	1 (0.5%)	29 (13%)	0
Fever	37 (17%)	1 (0.5%)	7 (3%)	0
Pain	37 (17%)	4 (2%)	22 (10%)	1 (0.5%)

Forty-one patients (18%) on the TICE® BCG arm experienced no toxicity vs. 69 patients (31%) on the MMC arm. Significant toxicity was slightly more common in the TICE® BCG arm (12% vs 8%); however, the

percent of patients discontinuing treatment because of toxicity was similar. Lower urinary tract irritative symptoms (frequency, urgency, dysuria, hematuria) were by far the most common serious toxicity with both drugs (69% vs 67%). Five deaths occurred on study: two on the TICE® BCG arm and three on the MMC arm. On review, none of the deaths appear to be study related.

PERTINENT ADVISORY COMMITTEE RECOMMENDATIONS

On December 16, 1996, the Oncologic Drugs Advisory Committee reviewed the data supporting the use of TICE® BCG for prophylaxis against recurrent papillary carcinoma of the urinary bladder. Initially, Organon Teknika Corporation made the following presentations:

Introduction - Dr. Michael Hanna, President
Overview of the safety and Efficacy Data - Dr. Donald Lamn
Conclusion - Dr. Donald Lamn

After the sponsor's comments, Dr. Sheldon Morris of the FDA presented a history of BCG and Dr. Richard Steffen summarized the FDA's review of the TICE® BCG data. The committee was then asked to consider five questions, proposed by the FDA, on the efficacy, safety, and infectious disease complications of using TICE® BCG to treat papillary tumors of the bladder (Summary Attached). Although the committee felt that the Nijmegen study did not provide evidence of the activity of TICE® BCG for this indication, the committee did agree that the SWOG study 8795 data did support the use of TICE® BCG in the prevention of TaT1 tumors. The committee also responded positively about the overall safety and effectiveness of TICE® BCG in the prophylactic therapy of tumors of the bladder. With respect to infectious disease concerns, the committee recommended that a more extensive discussion of infectious disease management, and especially the use of prophylactic isoniazid to treat inflammatory responses, should be included in the label.

APPROVED FINAL LABELING

The approved package insert is attached.

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