There was no significant difference between the two treatment arms with respect to number of treatment breaks.

Reviewer's comment 20. FDA Review of Missed Radiation Doses

One of the major problems with acute radiation toxicity is missed doses which limit the ability to deliver optimal treatment. There were a total of 497 missed doses among 132 patients in the A+RT arm and 425 missed doses among 131 patients in the RT arms. The following are the five most common reasons for missed radiation doses:

Table 23. Most Common Reasons for Missed Doses

Reason	A+RT (n=497)	RT (n=425)
Legal Holiday	178	187
Equipment Failure	102	98
Toxicity	99 (20%)	43 (10%)
Unknown	36	27
Missed Appointment	34	34

There were twice as much missed doses due to toxicity in the A+RT arm. (20% vs. 10%). Specific toxicities were not described in the database..

Reviewer's comment 21. FDA Review of Hospitalizations

Adverse events from treatment resulted in 101 hospitalizations in the A+RT arm and 63 hospitalizations in the RT alone arm involving twice as many patients in the A+RT arm [38 (25%) in the A+RT arm and 19 (12%) in the RT arm].

Laboratory Values Over Time

Statistically significant decreases in median hemoglobin (males), hematocrit (males), and calcium values ($p<0.0001$) were seen in the amifostine + RT arm versus the RT alone arm. At baseline, median hemoglobin (males), hematocrit (males), and calcium values were 13.6 g/dL, 40.5%, and 9.5 mg/dL, respectively; at the end of therapy, these values decreased to 13.0 g/dL, 39.6%, and 8.8 mg/dL, respectively. The median decreases in hemoglobin and hematocrit are maintained within the normal range.

SUPPORTING STUDIES

Reviewer's comment: *The following summaries of supporting studies were based on study reports submitted to the agency. Primary data was available only for the pivotal trial, WR-0038.*

Antonadou, et al[30] (Randomized Trial of the Prophylactic Use of Amifostine in the Prevention of Chemoradiation Induced Mucositis and Xerostomia in Head and Neck Cancer)

Design: Phase II randomized trial
Objective: To assess whether amifostine would protect against xerostomia and mucositis induced by radiochemotherapy (RCT). Mucositis and xerostomia were graded according to the RTOG/EORTC scoring criteria.
Treatment Schema: standard fractionated radiation therapy (2 Gy/day/5 days a week to a total dose of 60 to 74 Gy) and carboplatin (90 mg/m^2/week) with or without amifostine administered at a dose of 300 mg/m^2.
Follow-up: Monthly for 6 months. Tumor response analyzed on an intent-to-treat basis.
Patients: 45 patients (22 treated with amifostine + RCT, 23 treated with RCT alone), well balanced for age, gender, tumor type, TNM status
Late-Effect Xerostomia and Acute Mucositis

Radiation Toxicity/ RTOG Grade	Amifostine + RCT (n=22)		RCT (n=23)		p-Value
Late-Effect Xerostomia[b]					0.0001[a]
Grade 0	4	(18%)	0	—	
Grade 1	12	(55%)	4	(17%)	
Grade 2	6	(27%)	17	(74%)	
Grade 3	0	—	2	(9%)	
Total Grade 2	6	(27%)	19	(83%)	0.0001[c]
Grade 4 Mucositis					
Week 5	1	(5%)	12	(52%)	0.0001[c]
Week 6	4	(18%)	20	(87%)	<0.0001[c]
Week 7	8	(40%)	20	(95%)	0.0002[c]
Duration of Treatment					
Median	48 days		55 days		0.0127
Range	(42-60 days)		(42-74 days)		

[a] Based on Mantel-Haenszel Chi-square
[b] At 3 months post-radiation
[c] Based on Fishers exact test

Tumor Responses were evaluated at 6 weeks and 6 months post-treatment. There was no statistically significant difference between the two treatment arms (p=0.4140). At 6 months post-treatment, there were three local recurrences in the RCT alone arm and only one recurrence in the amifostine arm.

Reviewer's comment 22. Comments on the Antonadou study

- *Small sample size*
- *Other patient risk factors such as intent of radiotherapy, amount of organ exposure to radiation not well described.*
- *Radiation treatment plans and actual radiation doses were not described.*
- *Insufficient data for late xerostomia (3 months)*
- *Insufficient data on tumor recurrence to detect significant differences.*
- *Inadequate description of other adverse events*
- *Impressive findings on the comparison of the incidence of severe mucositis. The incidence of acute mucositis in the setting of radiochemotherapy should probably be investigated in larger randomized studies.*

Bohuslavizki, et al (Double-Blind Placebo-Controlled Study of Salivary Gland Protection by Amifostine in High-Dose Radioiodine Treatment)

Design: Double-blind, placebo-controlled, multiarm trial of HD-RIT ± amifostine in patients with differentiated thyroid cancer.
Objective: Quantitative salivary gland scintigraphy at 3 months after HD-RIT
Treatment Schema: Patients with differentiated thyroid cancer were randomized to receive HD-RIT plus pretreatment with 500 mg/m^2 of amifostine or HD-RIT plus placebo (physiologic saline solution). HD-RIT was either 3 GBq ^{131}I (n=21) as an initial treatment course or 6 GBq ^{131}I (n=29) as a second treatment course at least 6 months after the application of 3 GBq ^{131}I.
Patients: Tumor type and post-operative tumor staging were comparable
Results: There was a statistically significant ($p<0.0001$) decrease in Tc-99m-pertechnetate uptake of the parotid and submandibular glands 3 months after ablative RIT. However, there was minimal and insignificant reduction of parenchymal function of the parotid and submandibular glands.
Xerostomia: Nine patients (Grade 1), 2 patients (Grade 2) in the control arm, no reported xerostomia in the ethyol arm
Safety: There were significant differences relating to hypotension with "orthostatic collapse" in two patients that was managed with positioning of the patient and hydration.

Reviewer's comment 23. Comments on the Bohuslavizki study

- *The protocol did not describe the study endpoints in detail. The primary intent was to perform studies on the salivary gland that would document damage induced by high single doses of radiation seen in animals. There was no list of criteria for inclusion, no prospective description of clinical endpoints, follow-up plan and statistical analysis.*
- *Functional measurements of saliva production did not support significant findings from comparison of Tc-99m-pertechnetate uptake*
- *Inconclusive data for xerostomia*
- *Non-oncologic indication, results of thyroid function tests after treatment were not available*
- *Inadequate description of other adverse events*
- *This report did not contain sufficient relevant information to be supportive of the proposed indication*

Table 24. Summary of Benefits, Risks and Concerns

BENEFITS/ STRENGTHS	RISKS/ WEAKNESSES	CONCERNS/ UNCERTAINTIES
Study Design and Conduct • Large, randomized Phase 3 • Well-balanced population with respect to disease stage, parotid gland exposure, KPS and type of radiation • Usual daily fractionated RT dose given • RT Quality Assurance Team • DSI inspection OK	• Retrospective definition of efficacy analyses - clinically meaningful levels of saliva production and time categories for saliva collection analysis. • Small sample numbers for parotid saliva collection and scintigraphy analysis • Time to event analyses lack robustness due to few events at one year follow-up	• Should the trial have been placebo controlled? • Is one trial adequate? • Potential effect of numerous amifostine drop outs on efficacy endpoints • Is the data ruling out tumor protection adequate?
Efficacy • Significantly reduced ≥Gr2 acute xerostomia • Higher median cumulative RT dose before onset of ≥ Gr 2 acute xerostomia • Significant reduction in incidence of ≥Gr 2 late xerostomia • Significant difference in unstimulated saliva at one year using categorical cut-off identified by expert as clinically relevant. • PBQ: Trend towards better change from baseline, significant at end of treatment and one year follow-up. Significant difference in "general condition" among drop-outs • No difference in median survival among patients with rectal CA (supporting study)	• Patients in RT group received significantly higher total doses of radiation • No difference in overall incidence of acute and late xerostomia • No difference in stimulated saliva production • PBQ: Significant attrition/missing data, No difference in functional well-being and use of external aids • Weak evidence against tumor protection	
Safety	• 29 of 150 patients (19%) discontinued amifostine due to adverse events • Significantly greater frequency of known adverse events • More radiotherapy doses missed in the A+RT • More hospitalizations	

OVERALL EVALUATION AND CONCLUSIONS

The WR-0038 study was conducted in 40 centers, principally in the United States (U.S.), France, Germany, and Canada. Eligible patients included men or women, at least 18 years of age, undergoing definitive or adjuvant radiation therapy for histologically-confirmed squamous cell carcinoma of the head and neck. At least 75% of each parotid gland was present in the treatment fields. A total of 315 patients were randomized, 303 were treated, 150 patients in the A+RT arm and 153 patients in the RT arm. Patients were stratified by treatment center, site of disease, type of radiation, the presence of nodal disease and Karnofsky performance status and randomization was well-balanced between treatment arms.

Two of the three primary efficacy endpoints related to radiation involve assessment of ***acute*** events by investigators utilizing the RTOG Radiation Morbidity Scoring Criteria. There was no statistically significant difference in the incidence of Grade 3-4 acute mucositis ($p=0.48$), but there was a significant difference in the incidence of Grade 2-4 acute xerostomia in favor of Ethyol® (71% vs. 51%, $p<0.0001$). The third primary efficacy endpoint, ***late*** xerostomia, showed a significant difference in favor of the Ethyol ® arm in Grade 2-4 events (60% vs 33%, $p=0.0019$). The overall incidence of acute mucositis and late xerostomia (Grades 1-4) did not show a significant difference between treatment arms.

A secondary efficacy endpoint that provided support was post-treatment measurements of saliva production. Analysis of unstimulated saliva production according to a retrospective definition of clinically significant saliva production (≥ 0.1 gm) by the applicant showed that patients treated with Ethyol® produced more saliva compared to the control group one year after treatment (follow-up between six to 15 months). The difference in saliva production favored patients in the Ethyol® arm (63 patietns vs. 43 patients, $p=0.003$). This degree of difference in unstimulated saliva production was not seen in other post-treatment follow-up time points (3 and 6 months) nor in all stimulated saliva collections, including one year post-treatment. A longitudinal analysis by the FDA reviewer of unstimulated saliva production did not show any difference between treatment groups. In another anlaysis by the FDA looking at change from baseline saliva measurements, a trend in favor of the Ethyol® arm showing less change from baseline was present in the stimulated collections. Overall, the majority of the Advisory Committee agreed that the data on saliva production was supportive of the xerostomia results (12 to 1).

The data on the Patient Benefit Questionnaire (PBQ) were analyzed by the applicant and the FDA reviewer using different methods of retrospetively defined longitudinal analyses. The applicant evaluated the overall mean of the seven subscales of the PBQ and found significant differences in favor of Ethyol® at 7 months ($p=0.009$) and one year ($p=0.008$) after completion of therapy. The FDA reviewer's longitudinal analysis did not show a statistically significant difference in more specific parameters of "functional well-being", "general dryness" and "use of external aids"; but found trends in favor of Ethyol® . Again, the majority Advisory Committee voted in favor of the results of the PBQ being supportive (11 to 1).

The addition of Ethyol® to fractionated radiation resulted in significantly more but expected toxicies. There were significantly more severe side effects, more missed radiotherapy sessions

and more hospitalizations in the A+RT arm. Seventeen percent of patients discontinued Ethyol® due to adverse events; however, all but one continued to receive full doses of radiation. As one considers the effectiveness of anticancer therapy when combined with cytoprotective agents such as Ethyol®, the evidence against tumor protection by the cytoprotectant should be clear. In this case, the sponsor found no differences between the treatment arms in locoregional failure at 18 months [RT:A+RT 0.95 (0.64, 1.39], disease free survival [0.99 (0.69, 1.42)] and overall survival [1.35 (0.87, 2.1)]. Another study of patients with colorectal cancer (Liu, et al) showed similar two-year survival rates with and without Ethyol® after radiotherapy. During the advisory committee deliberations, the proposed indication was amended to include only patients being treated with post-operative radiotherapy. A minority of patients received definitive radiotherapy in the trial and since they tend to recur later, it was felt that there were too few patients and that their follow-up was too short. The committee voted 9 to 2 that there was adequate evidence that Ethyol® does not protect tumors during treatment of head and neck cancer with radiation therapy.

Overall, the efficacy findings in this application were found to be supportive of the proposed indication. However, another question that was posted was whether the strength of evidence from a single study would be adequate to support approval. The Advisory Committee voted 9 to 2 that Ethyol® should be approved "for the reduction of the incidence of moderate to severe xerostomia in patients undergoing post-operative treatment of head and neck cancer."

FINAL RECOMMENDATION

Supplemental NDA20-221 SE 012 for Ethyol should be approved to "decrease the incidence of moderate to severe xerostomia in patients receiving post-operative radiotherapy for head and neck cancer."

/S/ 6/22/99

Isagani Mario Chico, MD
Medical Officer
Division of Oncology
HFD-150

/S/ 6/24/99

TEAM LEADER

cc:
NDA #20-221
HFD-150/Division File
HFD-150/I.M. Chico
HFD-150/M. Pelosi

APPEARS THIS WAY
ON ORIGINAL

APPENDIX 1 ANSWERS TO ODAC QUESTIONS

NDA# 20-221/ SE-012

Ethyol for Radiation Induced Xerostomia in Head and Neck Cancer

June 8, 1999

This application seeks approval for Ethyol to "reduce the incidence of severe radiation induced xerostomia. (Severe being defined as ≥RTOG grade 2 acute and late xerostomia)."

Efficacy data come from a single multicenter, randomized, phase 3 trial in patients with head and neck cancer. It compares Ethyol plus standard fractionated radiotherapy (A+RT) with radiotherapy alone (RT) in 303 treated patients. Patient characteristics were generally well balanced on the study arms; however, patients randomized to the RT arm received higher total doses of radiation.

Xerostomia: The primary efficacy endpoints were acute and late xerostomia (grade 2 or higher) and acute mucositis (grade 3). There was no difference between the study arms in the incidence of acute grade 3 mucositis. However acute and late xerostomia (grade 2 or higher) were significantly more common on the RT-alone arm:

INCIDENCE OF XEROSTOMIA

	RT alone	A + RT	P value
Acute xerostomia	78% (120/153)	51% (75/148)	p < 0.0001
Late xerostomia	40% (63/153)	24% (36/150)	p = 0.0015

Although the patients on the RT + Ethyol arm received a higher median dose of radiation therapy than patients on the RT arm, when patients were grouped according to radiation dose received, an advantage for Ethyol was apparent in each group:

INCIDENCE OF LATE XEROSTOMIA

RT dose	RT alone	A + RT
<4500		0% (0/4)
4501-6500	43% (29/67)	19% (15/81)
>6500	40% (34/86)	32% (21/65)

1. Does this trial provided substantial evidence that Ethyol decreases the incidence of moderate-to-severe xerostomia in patients undergoing radiation treatment for head and neck cancer?

YES 11 NO 2

Salivary Measurements: Clinically meaningful levels of saliva production and time categories for saliva collection analysis were defined retrospectively. In the analysis of unstimulated saliva collection, the applicant used > 0.1 gram of saliva as the cutoff of adequate function, used the time window of one year's follow-up (defined as 6 to 15 months after treatment), and noted a significant difference in favor of the Ethyol arm (63 patients with adequate function on the Ethyol arm versus 43 patients on the RT arm,p = 0.003). The analysis of stimulated saliva collections by the applicant and longitudinal analysis of unstimulated saliva collections by the FDA did not show statistically significant differences between study arms.

2. Do the results of the salivary measurements provide supportive evidence that ethyol reduces the incidence and severity of late xerostomia?

YES 12 NO 1

Patient Benefit Questionnaire (PBQ): As described in the presentations, analytical plans for this parameter were submitted retrospectively. Consequently, the applicant and the Agency chose different methods of analysis. The applicant evaluated the overall mean of the 7 subscales of the PBQ and found statistically significant differences in favor of Ethyol 7 months (p=0.009) and 1 year (p=0.008) after completion of therapy. The longitudinal analyses by the FDA looked at three discrete areas identified by the reviewers as most clinically significant (functional well being, global assessment of dryness and use of external aids) and found trends in favor of Ethyol.

3. Do the results of the patient benefit questionnaire provide support to this application?

YES 11 NO 1 ABSTAIN 1

Tumor Control: In the evaluation of cytoprotective agents such as Ethyol, one must consider the adequacy of evidence demonstrating that the cytoprotective agent is not protecting the tumor from anticancer treatment. In this case, the FDA determined that relatively large trials in patients with head and neck cancer would be needed to rule out such a tumor protective effect relative to radiation therapy. The most relevant data submitted is from the randomized controlled study discussed above. In this trial no difference was noted between the arms in time to locoregional [RT:A+RT 0.95 (0.64, 1.39], disease free survival [0.99 (0.69, 1.42)] and overall survival [1.35 (0.87, 2.1)]. The lower bound of the 95% confidence intervals cannot exclude the possibility that

Ethyol is 36%, 31%, and 13% infererior, respectively. The sponsor also cites data from a 100-patient randomized study of Radiation Therapy +/- Ethyol in rectal cancer and data from a randomized trial of chemotherpay +/- Ethyol in ovarian cancer.

4. Is there adequate evidence that Ethyol does not protect tumors during *post-operative* treatment of head and neck cancer with radiation therapy

YES 9 NO 2 ABSTAIN 1

Safety Profile: There were significantly more severe adverse events, more missed radiotherapy sessions, and more hospitalizations in the A+RT arm. Adverse events attributed to Ethyol are listed in the following table:

Incidence of Treatment-Related Adverse Events Associated With Amifostine

Adverse Experience	A+RT (N=150) n	(%)	RT (N=153) n	(%)	P value
Nausea	66	(44%)	25	(16%)	**<0.0001**
Vomiting	55	(37%)	11	(7%)	**<0.0001**
Hypotension	22	(15%)	2	(1%)	**<0.0001**
Fever	12	(8%)	3	(2%)	**0.0174**
Allergic reaction	8	(5%)	0	—	**0.0033**
Dizziness/Lightheadedness	7	(5%)	0	—	**0.0068**

Approvability: Regulations require that substantial evidence of effectiveness be demonstrated through adequate and well-controlled investigations. In most cases, the FDA has required more than a single trial. As noted in the 1998 FDA Guidance for Industry, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products,* "In other cases, FDA has relied on only a single adequate and well-controlled efficacy study to support approval—generally only in cases in which a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study would have been difficult to conduct on ethical grounds."

5. Considering the efficacy evidence presented from this single randomized phase 3 study, considering the safety data, and considering the data on tumor protection, should Ethyol be approved "to decrease the incidence of moderate-to-severe xerostomia in patients undergoing *post-operative* radiation treatment for head and neck cancer?"

YES 9 NO 2

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commercial

information

block 2 cm wide and at least 2 cm in length on the skin surface will be placed in the anterior lower neck field to shield the larynx and the spinal cord in the junction region. For hypopharynx and larynx primaries, a lower lateral block, 2 cm in height should be placed in the lateral upper neck fields to shield the areas of potential overlap of diverging beams over the spinal cord. For nasopharyngeal primaries, a mid-line block is placed over the larynx to shield the larynx and spinal cord. Appropriate shielding should be done to exclude as much of the retro-orbital structures as possible without compromising the margins around the tumor.

The primary treatment fields should encompass the primary tumors with adequate margins along with known and/or suspected lymph node disease in the upper neck. There should be a minimum of a 2-3 cm margin around the primary tumor and positive nodes and should include upper neck nodes to be irradiated electively for the initial target volume.

additional posterior field may be necessary to deliver a supplemental dose to the positive nodes.
The lower border of the field will be just below the clavicle or 1 cm below the clavicle when there are positive nodes in the supraclavicular fossa.

Patients with clinically positive nodes greater than 6 cm, positive supraclavicular nodes or tumors that involve the pyriform sinus may be treated with large lateral fields to encompass the primary site and entire neck. A 5-15 degree table angle may be used to direct the "lateral" fields into the low neck region and upper mediastinum with the inferior borders below the level of the clavicular heads. An anterior supraclavicular field is not used in this technique.

Dose Calculation

Dose to the low anterior neck/supraclavicular field is calculated at 3 cm and to the upper mediastinum at 5 cm depth. Complete isodose curves are required. Lithium fluoride dosimetry is recommended as a further check on tumor dose. Cumulative isodose distributions at the level of tumor center, and a copy of the treatment record indicating cumulative doses, and boost field simulation and portal films must be submitted at the completion of radiotherapy. The specification of the target dose is in terms of a dose to a point at or near the center of target volume. The following portal arrangements are specified for photon beams:

For two opposed coaxial equally weighted beams: on the central ray at mid-separation of beams.

For arrangement of two or more intersecting beams: at the intersection of the central ray of the beams.

Other or complex treatment arrangements: at the center of the target area (Note: there may be several target areas).

Tissue equivalent compensators or wedges should be used to ensure homogeneity of dose distribution so that variation within the target volume and parotids does not exceed 10% of the target dose.

Boost doses will be specified at the actual sites of gross primary and nodal disease.

All fields will be treated once daily at 1.8 - 2.0 Gy per fraction, five days per week to a total dose of: post-operative low risk patients, 50-60 Gy; post-operative high risk patients, 60-66 Gy; definitive radiation patients, 66-70 Gy. Electrons should be used to boost nodal regions in the posterior neck when additional treatment to these regions is indicated. Fields must be reduced to exclude the spinal cord at 40-46 Gy at the midplane. However, the entire neck must be irradiated to a minimum dose of 46 Gy (even in Stage N_0) at anatomical levels of lymph node spread usually 2-4 cm below the skin surface. Positive neck nodes should receive a minimum dose of 60 Gy in 30-35 fractions in 6-7 weeks. To supplement the dose to the posterior neck and clinically positive nodes, boost techniques may include additional electron beam ($\geq$6 MeV) to the posterior neck, wedge pair or oblique fields. Initially clinically negative posterior neck nodes should receive a minimum dose of 44-46 Gy at 3 cm depth.

Time and Dose Modifications

Treatment breaks must be clearly indicated in the treatment record. Treatment breaks, if necessary, should not exceed five treatment days at a time and ten treatment days total and should be allowed only for healing of severe normal tissue reactions. Analysis of trial data will factor treatment breaks of longer duration. Treatment breaks of longer duration than outlined are NOT NECESSARILY reason to remove the patient from study.

Nutritional Support

In the event of excessive mucosal reaction and nutritional deterioration, nutritional support will be provided by means of i.v. fluids, hyperalimentation, NG tube feedings or percutaneous entero gastrostomy (PEG). The need for such nutritional support and the length of time required will be documented.

Duration of Treatment

Patients will be treated with radiation therapy for 5 days/week for 6-7 weeks (30-35 fractions) plus or minus amifostine prior to RT. For all patients registered, two reviews of radiation therapy were conducted. This review was coordinated by the Radiation Oncology Quality Assurance Center at the H. Lee Moffitt Cancer Center in Tampa, Florida. In the USA and Canada, the reviews were conducted by Drs. David Brizel and Todd Wasserman. In Europe, the reviews were conducted by Dr. Lusinchi at the Department of Radiotherapy, Institut Gustave-Roussy in Villejuif, France, with concurrence from Dr. Todd Wasserman and Dr. David Brizel.

Rapid Review: Within 5 days of radiation therapy to verify treatment planning in accordance with the protocol which includes: the prescription sheet for the entire treatment, simulation films for all treatment fields, port films for initial fields, representative MRI or CT scan sections, parotid and port drawing, photocopy of the PH2 form, diagrams of primary and nodal disease, calculation of initial fields, and partial daily treatment record.

Final Review: Within 1 week following completion of therapy: completed daily treatmetn record, additional simulation and portal films, composite isodose distribution, calculation sheets of all field modifications.

Appendix 4: Study Flow Chart

	Pre-Study		Weekly Evaluations Prior to Receiving Protocol Therapy							Monthly Follow-Up After Protocol Therapy											
Visit	Day -30	Day -14	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6/7	End of Protocol Therapy	M 1	M 3	M 5	M 7	M 9	M 11	M 13	M 15	M 17	M 19	M 21	M 23[c]
Medical History	X																				
Dental Exam	X																				
Notation of Concomitant Medications	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Effectiveness:																					
Assessment of Radiation Reactions[b]			X	X	X	X	X	X	X	X	X	X	X	X	X			X			X
Patient Questionnaire (PBQ)	X		X	X	X	X	X	X	X	X	X	X	X	X	X			X			X
Whole Saliva Sampling		X								X		X			X			X			X
Parotid Saliva Sampling[a]		X								X		X			X			X			X
Scintigraphy[a]		X								X		X			X			X			X
Tumor Assessment		X								X	X	X	X	X	X			X			X
Measurement of Clinically Palpable Disease		X			X				X	X	X	X	X	X	X			X			X
Chest X-ray	X																				
CT/MRI Head and Neck	X															X					X
CT of Liver/Bone Scan		X																			
Safety:																					
Other Radiation Toxicities[b]			X	X	X	X	X	X	X	X	X	X	X	X	X			X			X
Amifostine Toxicity Profile			X	X	X	X	X	X	X	X											
Physical Examination		X	X	X	X	X	X	X	X	X	X	X	X	X	X			X			X
Laboratory Assessments[d]		X							X												

[a] At selected institutions.
[b] Based on RTOG Acute and Late Radiation Morbidity Scoring Criteria.
[c] In year 2, patients were followed every 6 months.
[d] Includes complete blood count (CBC) with differential and platelets, and the following chemistry evaluations: glucose, calcium, albumin, total bilirubin, alkaline phosphatase, magnesium, SGOT, SGPT,
LDH, and serum creatinine.

Appendix 5. Patient Benefit Questionnaire (PBQ)

The questions below relate to the functioning of your salivary glands as a result of the radiation therapy to region)s) of your head and neck,. This questionnaire will be completed before treatment and at regular intervals during treatment and follow-up. You are asked to circle the number on the line indicating the severity of any problems you experience related to your treatment with "1" being a great deal of difficulty and "10" being none. If you are unclear about any of the questions, please ask your doctor or nurse to help you.

Example:
If your mouth is dry part of the time (such as only at night) you might circle "5". If your mouth is dry only at certain times such as during exercise, you might circle "8". The example below is marked as though you were dry only during a specific time as in the last statement.

1 2 3 4 5 6 7 (8) 9 10
Extremely Dry — Not Dry

1. Please rate the dryness of your mouth at rest (that is while not eating or chewing).
1 2 3 4 5 6 7 8 9 10
Extremely Dry — Not Dry

2. Please rate the soreness of your mouth.
1 2 3 4 5 6 7 8 9 10
Extreme Discomfort — Comfortable

3. Please rate the soreness of your tongue.
1 2 3 4 5 6 7 8 9 10
Extreme Discomfort — Comfortable

4. Please rate the discomfort of your dentures due to dryness.
1 2 3 4 5 6 7 8 9 10
Extreme Discomfort — Comfortable

5. Please rate the difficulty of your experience in your ability to talk due to dryness.
1 2 3 4 5 6 7 8 9 10
Extreme Discomfort — Comfortable

6. Please rate the difficulty you experience in your ability to chew and/or swallow due to dryness.
1 2 3 4 5 6 7 8 9 10
Extreme Discomfort — Comfortable

7. Rate the frequency of fluid intake to assist in eating. If you are unable to eat solid food, please check ____)
1 2 3 4 5 6 7 8 9 10
Extremely Frequent — None Required

8. Frequency of fluid intake required for comfort not associated with eating.
1 2 3 4 5 6 7 8 9 10
Extremely Frequent (each bite of food) — None Required

9. Rate any sleeping problems you have associated with oral dryness.
1 2 3 4 5 6 7 8 9 10
Extremely Problematic — None

MEDICAL OFFICER'S REVIEW OF AN NDA SUPPLEMENT

Ethyol® for the Reduction of the Incidence and Severity of Radiation-Induced Xerostomia

NDA # 20-221 S012

Submission Date:	**December 24, 1998**
Review completed:	**May 21, 1999**
Sponsor:	**U.S. Bioscience, Inc.**

Isagani Mario Chico, MD
Medical Reviewer

ABSTRACT

NDA application 20-221 presents data from 303 patients in a Phase 3 randomized, multicenter study supported by study reports from three studies with approximately 200 patients. Radiation can often lead to temporary or permanent damage to normal tissues. Acute xerostomia is a particularly bothersome symptom to patients; however, later radiation toxicities are often permanent and have profound effects on the patient's long-term health and well being. This application seeks approval for treatment with ethyol for reduction of the incidence and severity of radiation-induced xerostomia.

The objectives of the phase 3 study were to determine if the addition of ethyol to standard fractionated radiotherapy reduced the incidence of oral radiation toxicities without decreasing antitumor efficacy. Patients with squamous cell carcinoma were stratified according to site of disease, nodal status, Karnofsky Performance Status, percent of the parotid glands in the radiation fields, and type of radiation. Each was randomized to receive RT (1.8 to 2.0 Gy 5 days/week for 6-7 weeks) ± ethyol (200 mg/m^2 i.v. prior to RT). Primary efficacy endpoints include the reduction of grade 2-4 acute and late xerostomia, and grade 3-4 acute mucositis. Secondary endpoints include measurement of whole saliva production and parotid saliva production, time to onset and duration of xerostomia and mucositis, patient benefit analysis through a patient benefit questionnaire (PBQ) and locoregional tumor control at one year. A total of 315 patients were randomized, with 150 patients in the amifostine + radiotherapy arm (A+RT) and 153 patients in the radiotherapy only (RT) arm included in the intent to treat analysis.

Pretreatment patient characteristics were balanced; however, during the study, patients in the RT arm received significantly higher total doses of radiation. Using the intent to treat analysis, the incidence of severe acute and late xerostomia was significantly reduced in the A+RT arm. There was no significant difference in acute mucositis and overall incidence of acute and late xerostomia. Unstimulated saliva collections showed a significant advantage for ethyol at the one year follow-up analysis but this was not confirmed by data from stimulated saliva collections and the FDA analysis using comparisons with mean baseline measurements. Analysis of clinical benefit from the patient benefit questionnaire did not yield significant findings. Analysis of locoregional tumor control, disease free survival and overall survival are limited by high censor rates and small number of events.

Monitoring of adverse events showed expected but significantly higher incidences of nausea, vomiting, hypotension, fever, allergic reaction, dizziness and lightheadedness despite lower daily doses of ethyol. Nineteen percent of patients discontinued ethyol due to adverse events, there were more skipped treatments and more hospitalizations due to adverse events in the ethyol arm.

SUMMARY OF BENEFITS, RISKS AND CONCERNS

BENEFITS/ STRENGTHS	RISKS/ WEAKNESSES	CONCERNS/ UNCERTAINTIES
Study Design and Conduct • Large, randomized Phase 3 • Well-balanced population with respect to disease stage, parotid gland exposure, KPS and type of radiation • Usual daily fractionated RT dose given • RT Quality Assurance Team • DSI inspection OK	• Retrospective definition of efficacy analyses: - clinically meaningful levels of saliva production and time categories for saliva collection analysis • Small sample numbers for parotid saliva collection and scintigraphy analysis • Time to event analyses lack robustness due to few events at one year follow-up	• Should the trial have been placebo controlled? • Is one trial adequate? • Potential effect of large amifostine drop outs on efficacy endpoints • Is the data ruling out tumor protection adequate?
Efficacy • Significantly reduced ≥Gr2 acute xerostomia • Higher median cumulative RT dose before onset of ≥ Gr 2 acute xerostomia • Significant reduction in incidence of ≥Gr 2 late xerostomia • Significant difference in unstimulated saliva at one year using categorical cut-off identified by expert as clinically relevant. • PBQ: Trend towards better change from baseline, significant at end of treatment and one year follow-up. Significant difference in "general condition" among drop-outs • No difference in median survival among patients with rectal CA (supporting study)	• Patients in RT group received significantly higher total doses of radiation • No difference in overall incidence of acute and late xerostomia • No difference in stimulated saliva production • PBQ: Significant attrition/missing data, No difference in functional well-being and use of external aids • Weak evidence against tumor protection	
Safety	• 29 of 150 patients (19%) discontinued amifostine due to adverse events • Significantly greater frequency of known adverse events • More radiotherapy doses missed in the A+RT • More hospitalizations	

Ethyol® (amifostine)

NDA #20-221
Radiotherapy SNDA #012

4-Month Safety Update

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Introduction

This section has been updated to comply with the requirements for a 4-month safety update report, and includes additional information learned about the safety of amifostine since the submission of the original SNDA #012 on December 23, 1998. In the original SNDA, all safety information pertaining to amifostine was presented in Section H: Integrated Summary of Safety, and contained safety information through a cut-off date of December 10, 1998. This 4-month safety update report contains new safety information through a cut-off date of April 12, 1999.

Since the December 10, 1998 cut-off, total patient exposure has not substantially changed. Data are available for an additional 89 patients who have received amifostine in clinical trials sponsored by U.S. Bioscience. These include 27 patients in the Phase III trial WR-0053, 35 patients in the Phase III trial WR-0056, and 27 patients in the Phase II trial WR-B058; all three of these studies are categorized as chemotherapy trials. The addition of these data to the U.S. Bioscience safety database has revised the following tables which were presented in the original SNDA: TABLE 25A (Extent of Exposure to Amifostine in Chemotherapy Studies) and TABLE 28A (Incidence of Adverse Experiences Related to Amifostine by Dose - Chemotherapy Studies). Specifically, these revisions can be found in the 740 to 910 mg/m^2 and <740 mg/m^2 dose groups. As shown in the updated TABLE 28A, the data show no clinically relevant differences between the safety data in the original SNDA and this 4-month safety update.

The number of post-marketing serious adverse events filed to the United States Food and Drug Administration (FDA) as 15-day Alert Reports was also updated in this report. A total of 254 additional events have been reported during the 4-month safety update period. These changes are reflected in TABLE 39 of this report. As shown in this table, there were no significant changes in the frequency of post-marketing serious adverse events as reflected in this 4-month safety update.

The safety data for the Phase III, pivotal trial WR-0038, was presented in full in the original SNDA (submitted December 23, 1998). In addition, the 12-month data on local regional tumor control (LRC) and survival (disease free and overall) for available patients were presented in Section H: Integrated Summary of Safety under Subsection 10, Drug-Demographic and Drug-Disease Interactions. Contained in this safety update report is the 18-month data on LRC and survival (disease free and overall) for available patients. These data are presented at the end of this report in an update to the section on Drug-Demographic and Drug-Disease Interactions. The data show that at 18 months, LRC and disease free survival remain comparable between treatment arms, supporting preservation of antitumor activity by amifostine. In addition, although not statistically significant, a trend towards improvement in overall survival remains in the amifostine arm.

Update to Overall Extent of Exposure in Clinical Trials

As of April 12, 1999, over 1,400 cancer patients have received more than 12,900 infusions of amifostine prior to chemotherapy (1,143 patients; 6,132 infusions), radiation therapy (226 patients; 5,685 infusions), or combined chemotherapy and radiotherapy (60 patients; 1,116 infusions) in clinical trials sponsored by U.S. Bioscience or other trials for which U.S. Bioscience had access to raw safety data. These updated numbers include the additional 89 patients in chemotherapy studies who received over 900 infusions of amifostine. Twenty-seven of these 89 patients received amifostine at doses <740 mg/m^2 and the remaining 62 patients received amifostine at doses ranging from 740 to 910 mg/m^2. These updated numbers are presented in TABLE 25A. Adverse event data corresponding to these patients can be found in TABLE 28A.

TABLE 25A

Extent of Exposure to Amifostine in Chemotherapy Studies[a]

	Dose (mg/m^2)				
Duration[b] (Exposures)	<740	740-910	>910	Total (Any Dose)	(%)
1	11	152	7	170	15%
2-3	24	344	6	374	33%
4-6	11	382	7	400	35%
7-9	1	60	0	61	5%
>9	63	75	0	138	12%
Total (Any Duration)	110	1013	20	1143	100%
(%)	10%	89%	2%	100%	

The chemotherapy studies are as follows: WR-0001, WR-0002, WR-0003, WR-0032, WR-0053, WR-0056, WR-9002, WR-9004, WR-9005, WR-9512, WR-9513, WR-9516, WR-9519, WR-A005, WR-A006, WR-A014, WR-A035, WR-A044, WR-A045, WR-A052, WR-A057, WR-B001, WR-B002, WR-B003, WR-B004, WR-B008, WR-B011, WR-B017, WR-B018, WR-B019, WR-B023, WR-B025, WR-B026, WR-B027, WR-B029, WR-B058, WR-B501, WR-B506, WR-B509, and WR-C010.

[a] Includes an additional 89 patients who received over 900 infusions of amifostine as of April 12, 1999.

[b] Duration was based on number of exposures (doses) of amifostine received for a particular study.

Update to By-Dose Analysis of Adverse Events Associated With Amifostine

TABLE 28A displays the incidence of adverse experiences related to amifostine by dose in chemotherapy studies. This table has been updated due to the fact that the additional 89 patients in the April 12, 1999 U.S. Bioscience safety database are enrolled in chemotherapy trials. In comparing the two safety databases (December 10, 1998 and April 12, 1999), the frequency (per patient, per infusion, and per discontinuation) of adverse events are comparable.

TABLE 28A

Incidence of Adverse Experiences Related to Amifostine by Dose
- Chemotherapy Studies -
(Clinical Database as of April 12, 1999)

	Adverse Events Per Patient		Adverse Events Per Infusion		Patients Who Discontinued Amifostine	
Adverse Experience (All Grades)	n	%	n	%	n	%
>910 mg/m²	**(n = 20)**		**(n = 57)**			
Nausea/Vomiting	19	95.0	45	78.9	0	—
Flushing/Feeling of Warmth	15	75.0	28	49.1	0	—
Hypotension	13	65.0	19	33.3	0	—
Sneezing	11	55.0	23	40.4	0	—
Dizziness/Lightheadedness	5	25.0	6	10.5	0	—
Sleepiness/Somnolence	5	25.0	8	14.0	0	—
Hypocalcemia	1	5.0	1	1.8	0	—
740 to 910 mg/m²	**(n = 1013)**		**(n = 4337)**			
Nausea/Vomiting	806	79.6	2710	62.5	22	2.2
Hypotension	414	40.9	747	17.2	20	2.0
Flushing/Feeling of Warmth	338	33.4	649	15.0	1	0.1
Sneezing	240	23.7	502	11.6	0	—
Fatigue/Lethargy	213	21.0	361	8.3	11	1.1
Fever	156	15.4	306	7.1	2	0.2
Dizziness/Lightheadedness	133	13.1	181	4.2	3	0.3
Hiccups	55	5.4	75	1.7	0	—
Sleepiness/Somnolence	45	4.4	58	1.3	0	—
Chills/Rigors	36	3.6	43	1.0	0	—
Allergy/Rash	14	1.4	14	0.3	1	0.1
Hypocalcemia	7	0.7	7	0.2	0	—
<740 mg/m²	**(n = 110)**		**(n = 1738)**			
Nausea/Vomiting	48	43.6	92	5.3	2	1.8
Hypotension	16	14.5	37	2.1	0	—
Flushing/Feeling of Warmth	11	10.0	32	1.8	0	—
Dizziness/Lightheadedness	10	9.1	15	0.9	0	—
Fatigue/Lethargy	9	8.2	21	1.2	0	—
Sleepiness/Somnolence	8	7.3	13	0.7	0	—
Sneezing	8	7.3	9	0.5	0	—
Allergy/Rash	6	5.5	6	0.3	1	0.9
Fever	3	2.7	3	0.2	0	—
Chills/Rigors	1	0.9	1	0.1	0	—
Hypocalcemia	1	0.9	1	0.1	0	—

Update to Adverse Events From Sources Other Than Clinical Trials

As of April 12, 1999, Ethyol® (amifostine) had been approved for marketing in 50 countries worldwide. It is estimated that approximately 750,000 vials of amifostine have been distributed worldwide. Assuming that on average three vials are given per patient per infusion (for a dose of 740 to 910 mg/m^2), approximately 250,000 patient treatments (infusions) have been administered, encompassing use in clinical trials and post-marketing experience. This represents an increase of approximately 65,000 patient treatments over that reported in the original SNDA.

As of April 12, 1999, a total of 1,549 events have been reported to the FDA in the context of 15-Day Alert Reports of spontaneous post-marketed adverse drug reactions. This represents an additional 254 events from those cited in the original SNDA.

TABLE 39 contains an updated comprehensive list of the adverse events reported to the FDA since amifostine was marketed, through a cut-off date of April 12, 1999. As indicated by asterisks in TABLE 39, a total of 24 new adverse event terms have been reported since the December 10, 1998 cut-off used in the original SNDA. These events occurred at very low frequencies (<0.3%), and do not represent a significant change in the safety profile of the drug. It should be noted that the frequency pertains to the number of events, not the number of patients.

The most frequently reported events are as follows: nausea (12%), vomiting (11%), hypotension (9%), flushing (3%), sweating increased (2%), dyspnoea (2%), dizziness (2%), and fever (2%). All other events described occur at a frequency of <2%. These findings are consistent with those observed in the December 10, 1998 safety database and are adequately described in the proposed prescribing information.

TABLE 39

Summary of 15-Day Alert Post-Marketing Adverse Events Reported for Amifostine as of April 12, 1999 (Coded Terms)

Body System/Adverse Event	Frequency of Adverse Events N	%
Application Site Disorders		
Application Site Reaction	1	0.06%
Autonomic Nervous System Disorders		
Flushing	1	0.06%
Hypertension	1	0.06%
Hypotension	9	0.58%
Pallor	2	0.13%
Urinary Incontinence	2	0.13%
Vomiting	10	0.65%
Body as a Whole - General Disorders		
Abdomen Enlarged	1	0.06%
Abdominal Pain	2	0.13%
Allergic Reaction	16	1.03%
Anaphylactic Shock*	1	0.06%
Ascites	4	0.26%
Asthenia	11	0.71%
Chest Pain	6	0.39%
Chest Pain Substernal	1	0.06%
Chills	3	0.19%
Condition Aggravated	3	0.19%
Death	6	0.39%
Disease Progression	4	0.26%
Drug-Food Interaction	1	0.06%
Face Oedema	1	0.06%
Fatigue	5	0.32%
Fever	33	2.13%
Hot Flushes	1	0.06%
Influenza-Like Symptoms	1	0.06%
Malaise	17	1.10%
Oedema	1	0.06%
Oedema Generalized*	1	0.06%
Oedema Mouth	2	0.13%
Oedema Peripheral	2	0.13%
Pain	8	0.52%
Pallor	18	1.16%
Rigors	24	1.55%
Syncope	12	0.77%
Temperature Changed Sensation	1	0.06%
Therapeutic Response Decreased	3	0.19%

* Represents new term reported since December 10, 1998.

TABLE 39

Summary of 15-Day Alert Post-Marketing Adverse Events Reported for Amifostine as of April 12, 1999 (Coded Terms)

	Frequency of Adverse Events	
Body System/Adverse Event	**N**	**%**
Cardiovascular Disorders, General		
Cardiac Failure	2	0.13%
Circulatory Failure	1	0.06%
Cyanosis	3	0.19%
ECG Abnormal Specific	1	0.06%
Hypertension	10	0.65%
Hypotension	140	9.04%
Oedema Peripheral	1	0.06%
Pulmonary Oedema	1	0.06%
Pulse Weak	1	0.06%
Syncope	4	0.26%
Central & Peripheral Nervous System Disorders		
Aphasia	2	0.13%
Brain Stem Disorder	3	0.19%
Coma	2	0.13%
Confusion	2	0.13%
Convulsions	9	0.58%
Convulsions Grand Mal	1	0.06%
Cramps Legs	1	0.06%
Dizziness	33	2.13%
Dysesthesia	1	0.06%
Extrapyramidal Disorder	2	0.13%
Headache	5	0.32%
Hemiplegia	1	0.06%
Hyperkinesia	3	0.19%
Hypertonia	1	0.06%
Hypesthesia	2	0.13%
Hypotonia	1	0.06%
Muscle Contractions Involuntary	4	0.26%
Neuritis	1	0.06%
Neuropathy	2	0.13%
Neuropathy Peripheral*	1	0.06%
Paraesthesia	15	0.97%
Paraplegia*	1	0.06%
Sensory Disturbance	1	0.06%
Stupor	2	0.13%
Tetany	2	0.13%
Tremor	5	0.32%
Collagen Disorders		
Vasculitis	1	0.06%
Endocrine Disorders		
Hyperthyroidism	1	0.06%
Thyroiditis	1	0.06%
Foetal Disorders		
Hydrocephalus	1	0.06%

* Represents new term reported since December 10, 1998.

TABLE 39

Summary of 15-Day Alert Post-Marketing Adverse Events Reported for Amifostine as of April 12, 1999 (Coded Terms)

Body System/Adverse Event	Frequency of Adverse Events N	%
Gastrointestinal System Disorders		
Abdominal Pain	8	0.52%
Anorexia	3	0.19%
Diarrhea	8	0.52%
Diarrhea, *Clostridium Difficile**	2	0.13%
Dysphagia	3	0.19%
Hiccup	12	0.77%
Intestinal Necrosis*	2	0.13%
Mouth Dry	2	0.13%
Mucositis NOS	7	0.45%
Nausea	189	12.20%
Stomatitis Ulcerative*	1	0.06%
Vomiting	167	10.78%
Hearing and Vestibular Disorders		
Hearing Decreased	1	0.06%
Heart Rate and Rhythm Disorders		
Arrhythmia	4	0.26%
Arrhythmia Atrial	1	0.06%
Arrhythmia Ventricular	2	0.13%
Bradycardia	2	0.13%
Cardiac Arrest	5	0.32%
Fibrillation Atrial	5	0.32%
Palpitation	4	0.26%
Tachycardia	9	0.58%
Tachycardia Supraventricular	1	0.06%
Liver and Biliary Systems		
Bilirubinaemia	3	0.19%
Hepatic Enzymes Increased	4	0.26%
Hepatic Failure	2	0.13%
Hepatic Necrosis*	2	0.13%
Hepatitis	2	0.13%
Hepatitis Viral	1	0.06%
Jaundice*	2	0.13%
Liver Fatty	2	0.13%
SGOT Increased	3	0.19%
SGPT Increased	3	0.19%

* Represents new term reported since December 10, 1998.

TABLE 39

Summary of 15-Day Alert Post-Marketing Adverse Events Reported for Amifostine as of April 12, 1999 (Coded Terms)

	Frequency of Adverse Events	
Body System/Adverse Event	**N**	**%**
Metabolic and Nutritional Disorders		
Acidosis Lactic	4	0.26%
BUN Increased	6	0.39%
Cachexia	1	0.06%
Dehydration	19	1.23%
Diabetes Mellitus	1	0.06%
Diabetes Mellitus Aggravated	1	0.06%
Gout*	1	0.06%
Hyperglycaemia	4	0.26%
Hyperkalaemia	2	0.13%
Hypervolaemia	1	0.06%
Hypocalcaemia	13	0.84%
Hypochloraemia	1	0.06%
Hypokalaemia	8	0.52%
Hypomagnesaemia	8	0.52%
Hyponatremia	2	0.13%
Hypophosphataemia	1	0.06%
LDH Increased	3	0.19%
NPN Increased	21	1.36%
Oedema Generalized	3	0.19%
Oedema Periorbital	1	0.06%
Oedema Pharynx	1	0.06%
Thirst	1	0.06%
Weight Increase	1	0.06%
Musculoskeletal System Disorders		
Arthralgia	3	0.19%
Arthritis*	1	0.06%
Arthropathy*	1	0.06%
Back Pain	1	0.06%
Muscle Weakness	5	0.32%
Myalgia	2	0.13%
Skeletal Pain	1	0.06%
Myo-Endo Pericardial & Valve Disorders		
Angina Pectoris	1	0.06%
Myocardial Infarction	5	0.32%
Myocardial Ischaemia	1	0.06%
Pericarditis	1	0.06%

* Represents new term reported since December 10, 1998.

TABLE 39

Summary of 15-Day Alert Post-Marketing Adverse Events Reported for Amifostine as of April 12, 1999 (Coded Terms)

Body System/Adverse Event	Frequency of Adverse Events N	%
Platelet, Bleeding & Clotting Disorders		
Coagulation Disorder*	1	0.06%
Disseminated Intravascular Coagulation*	1	0.06%
Embolism Pulmonary	4	0.26%
Gastrointestinal Hemorrhage*	1	0.06%
Haematemesis*	1	0.06%
Haematoma*	2	0.13%
Haemorrhage Intracranial	1	0.06%
Haemorrhage NOS	2	0.13%
Prothrombin Decreased	2	0.13%
Prothrombin Increased	1	0.06%
Purpura	1	0.06%
Thrombocytopenia	11	0.71%
Thrombosis	2	0.13%
Psychiatric Disorders		
Agitation	5	0.32%
Anorexia	4	0.26%
Anxiety	5	0.32%
Confusion	7	0.45%
Delirium	1	0.06%
Dementia	1	0.06%
Hallucination*	1	0.06%
Insomnia	1	0.06%
Nervousness	3	0.19%
Somnolence	21	1.36%
Thinking Abnormal	2	0.13%
Red Blood Cell Disorders		
Anaemia	12	0.77%
Anaemia Haemolytic	1	0.06%
Haemolysis	1	0.06%
Marrow Depression	1	0.06%
Pancytopenia	2	0.13%
Reproductive Disorders, Female		
Vaginitis	1	0.06%
Resistance Mechanism Disorders		
Infection	1	0.06%
Infection Fungal*	4	0.26%
Moniliasis	3	0.19%
Sepsis	8	0.52%

* Represents new term reported since December 10, 1998.

TABLE 39

Summary of 15-Day Alert Post-Marketing Adverse Events Reported for Amifostine as of April 12, 1999 (Coded Terms)

Body System/Adverse Event	Frequency of Adverse Events N	%
Respiratory System Disorders		
Apnoea	2	0.13%
Bronchospasm	3	0.19%
Chronic Obstruct Airways Disease	1	0.06%
Coughing	11	0.71%
Cyanosis	1	0.06%
Dyspnoea	33	2.13%
Hemothorax*	1	0.06%
Hypoventilation	3	0.19%
Hypoxia	11	0.71%
Larynx Oedema	2	0.13%
Pharyngitis	1	0.06%
Pleural Effusion	2	0.13%
Pleurisy	1	0.06%
Pneumonia	6	0.39%
Pneumothorax	1	0.06%
Pulmonary Congestion	2	0.13%
Pulmonary Infiltration	2	0.13%
Pulmonary Oedema	1	0.06%
Respiratory Depression	5	0.32%
Respiratory Insufficiency	1	0.06%
Rhinitis	25	1.61%
Sneezing	1	0.06%
Stridor	2	0.13%
Throat Tightness	4	0.26%
Yawning	1	0.06%
Skin and Appendages Disorders		
Acne	1	0.06%
Bullous Eruption	1	0.06%
Dermatitis*	2	0.13%
Dermatitis Lichenoid*	1	0.06%
Epidermal Necrolysis	6	0.39%
Erythema Multiforme*	2	0.13%
Pruritus	8	0.52%
Rash	14	0.90%
Rash Erythematous	10	0.65%
Rash Maculo-papular	7	0.45%
Skin Cold Clammy	2	0.13%
Skin Disorder	1	0.06%
Skin Dry	1	0.06%
Skin Exfoliation	1	0.06%
Sweating Increased	30	1.94%
Urticaria	2	0.13%
Special Senses Other, Disorders		
Taste Perversion	1	0.06%

* Represents new term reported since December 10, 1998.

TABLE 39

Summary of 15-Day Alert Post-Marketing Adverse Events Reported for Amifostine as of April 12, 1999 (Coded Terms)

	Frequency of Adverse Events	
Body System/Adverse Event	**N**	**%**
Urogenital System Disorders		
Anuria	1	0.06%
BUN Increased	1	0.06%
Creatinine Blood Increased	6	0.39%
Haematuria	1	0.06%
Micturition Frequency	3	0.19%
Nephropathy Toxic	2	0.13%
NPN Increased	1	0.06%
Oliguria	1	0.06%
Polyguria	1	0.06%
Renal Failure Acute	17	1.10%
Renal Function Abnormal	5	0.32%
Renal Tubular Disorder	5	0.32%
Uraemia	1	0.06%
Urinary Incontinence	9	0.58%
Urinary Tract Infection	3	0.19%
Vascular (Extracardiac) Disorders		
Cerebrovascular Disorder	2	0.13%
Flushing	44	2.84%
Purpura	1	0.06%
Thrombophlebitis	1	0.06%
Vision Disorders		
Anisocoria	2	0.13%
Conjunctivitis	1	0.06%
Diplopia	1	0.06%
Eye Pain	2	0.13%
Ocular Haemorrhage	1	0.06%
Papilloedema	1	0.06%
Vision Abnormal	7	0.45%
White Cell and RES Disorders		
Granulocytopenia	9	0.58%
Leucopenia	7	0.45%
Leukocytosis	2	0.13%
Lymphoma-Like Disorder	1	0.06%
Lymphopenia	2	0.13%
Neutropenia*	4	0.26%
Pancytopenia	2	0.13%
TOTAL	**1549**	**100.00%**

* Represents new term reported since December 10, 1998.

Update to Drug-Demographic and Drug-Disease Interactions

The 18-month data on local regional tumor control (LRC) and survival for the Phase III, pivotal trial WR-0038 were analyzed as of April 21, 1999. Data are available on 259 patients (126 in the amifostine arm and 133 patients on the RT alone arm) for the LRC rate and all 303 patients (150 in the amifostine arm and 153 patients in the RT alone arm) for disease free and overall survival. In the original SNDA, data were available on 262 patients for LRC rate (127 in the amifostine arm and 135 patients on the RT alone arm) and all 303 patients for disease free and overall survival.

As shown below, the 18-month data demonstrate that amifostine continues to preserve the antitumor efficacy of radiation.

- **Study WR-0038: Phase III Randomized Trial of Radiation ± Ethyol (Amifostine) in Patients With Head and Neck Cancer:**

  12-Month Data:

  - LRC at 1 year was 72% in the Ethyol + RT arm and 71% in the RT alone arm, with LRC ratio and 95% confidence limits of 1.008 (0.864, 1.175)

    T-stage and radiation type were significant prognostic factors for locoregional tumor control at 1 year (p=0.0054 and p=0.0002, respectively). After adjusting for these factors, the odds ratio of locoregional control at 1 year for Ethyol + RT/RT alone was 0.990.

  - Disease-free survival at 1 year was 74.6% in the Ethyol + RT arm and 70.4% in the RT alone arm, with hazard ratio and 95% confidence limits of 1.035 (0.702, 1.528)

    The significant prognostic factors for disease-free survival were T-stage (0.0004), radiation type (p<0.0001), and radiation dose (p=0.0065). After adjusting for these factors, the hazard ratio of RT alone/Ethyol + RT was 1.038.

  - Survival at 1 year was 89.4% in the Ethyol + RT arm and 82.4% in the RT alone arm, with hazard ratio and 95% confidence limits of 1.585 (0.961, 2.613)

    The significant prognostic factors for survival were T-stage (p=0.0041), radiation type (p=0.0006), performance status (p=0.0022), and radiation dose (p=0.0014). After adjusting for these factors, the hazard ratio of RT alone/Ethyol + RT was 1.726.

18-Month Data:

- LRC at 18 months is 61% in the Ethyol + RT arm and 64% in the RT alone arm, with LRC ratio and 95% confidence limits of 0.956 (0.792, 1.155)

  T-stage and radiation type were significant prognostic factors for locoregional tumor control at 18 months ($p=0.026$ and $p<0.001$, respectively). After adjusting for these factors, the odds ratio of locoregional control at 18 months for Ethyol + RT/RT alone was 0.951.

- Disease-free survival at 18 months is 63.3% in the Ethyol + RT arm and 62.8% in the RT alone arm, with hazard ratio and 95% confidence limits of 0.990 (0.689, 1.423); these data are shown graphically in FIGURE A on the following page.

  The significant prognostic factors for disease-free survival were T-stage (0.0007), radiation type ($p<0.001$), and radiation dose ($p=0.0116$). After adjusting for these factors, the hazard ratio of RT alone/Ethyol + RT was 0.981.

- Survival at 18 months is 81.3% in the Ethyol + RT arm and 72.7% in the RT alone arm, with hazard ratio and 95% confidence limits of 1.351 (0.865, 2.109); these data are shown graphically in FIGURE B on the following page.

  The significant prognostic factors for survival were T-stage ($p=0.0022$), radiation type ($p<0.001$), performance status ($p=0.0037$), and radiation dose ($p=0.0080$). After adjusting for these factors, the hazard ratio of RT alone/Ethyol + RT was 1.413.

WR−38: Progression Free Survival

(Intent to Treat)

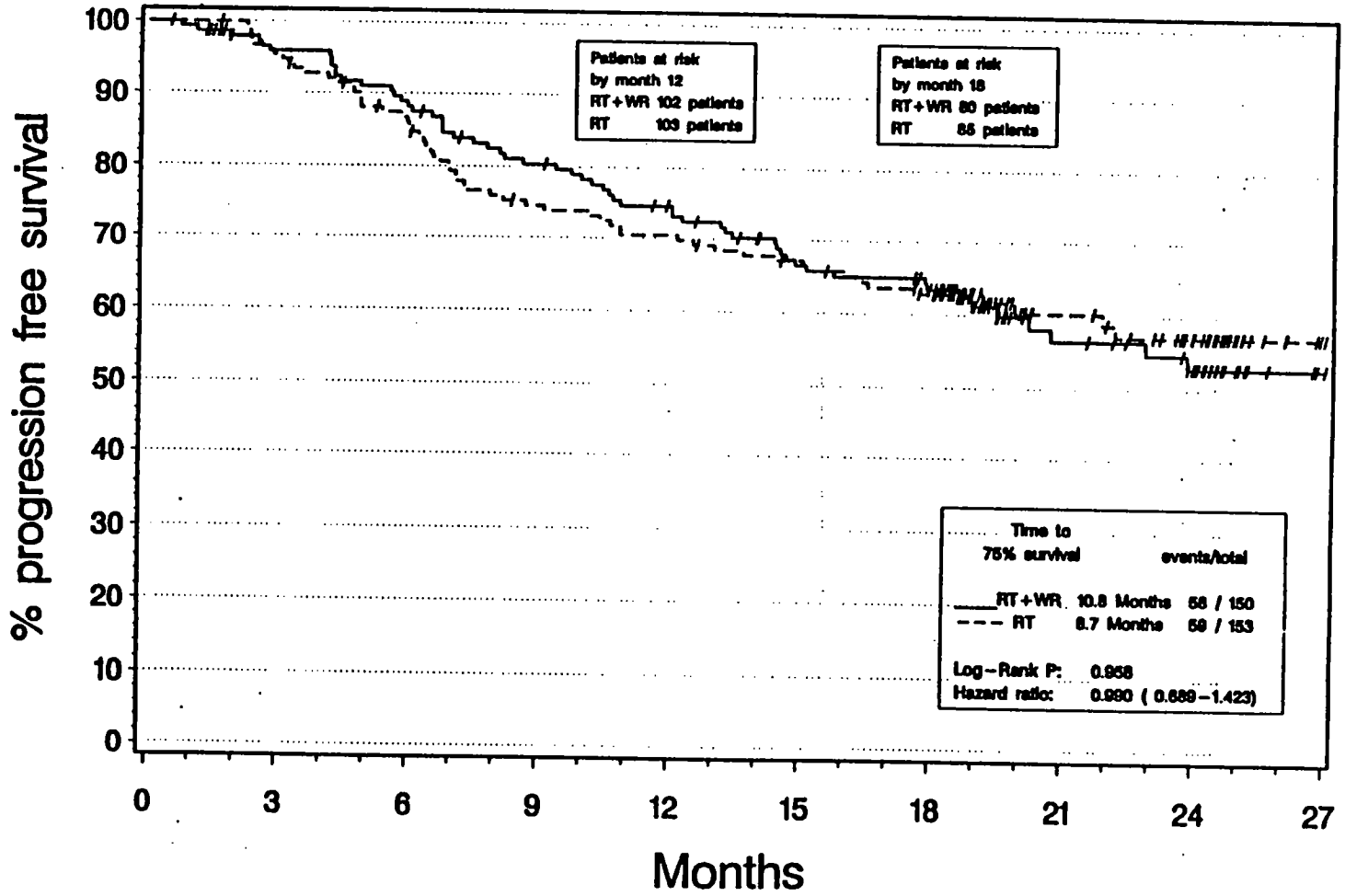

FIGURE A: 18-Month Disease-free survival curves of patients with RT ± Ethyol (WR) for head and neck cancer.

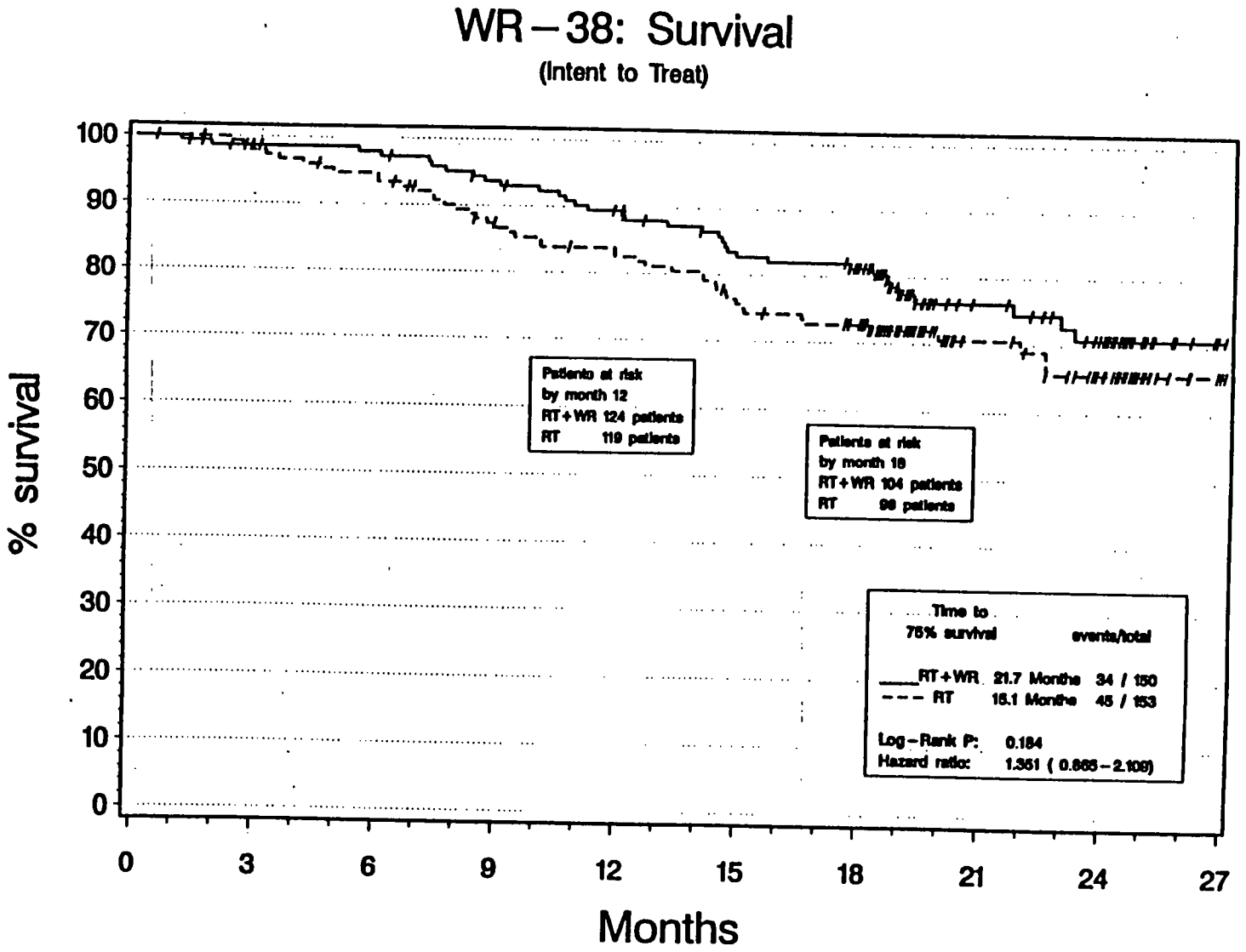

FIGURE B: 18-Month survival curves of patients with RT ± Ethyol (WR) for head and neck cancer.

**** SOURCE: STAT:[PROTOCOL.WR0038]GH_SURV.SAS;45 ****
21APR99 15:05

Updated Literature Search

A comprehensive literature search update was performed, using the same parameters as described in the original SNDA, for the time period December 17, 1998 to April 13, 1999. This period covers new information published since the submission of the SNDA. There were no reports of significant safety findings identified from preclinical or clinical studies conducted with amifostine. Following is a review of the literature published between this time period, along with a discussion of the relevancy to the currently approved use or the use of amifostine as proposed in the SNDA.

The results from a study conducted by Hoper, *et al* [Strahlentherapie Und Onkologie, Jan 1999, Vol.175 (1), p.28-31], show that amifostine induced an increase in vascular density in the rapidly proliferating area vasculosa of the early chick embryo. The relevance of this study to amifostine is at this stage unclear.

Nazeyrollas, *et al* [Cancer Chemotherapy and Pharmacology, 1999, Vol.43 (3), p.227-232], studied the effects of amifostine in a perfused isolated Langendorff-type model of rat heart. The results showed that amifostine induced coronary dilation, and displayed a protective effect against acute doxorubicin-induced cardiotoxicity. These results are not particularly new findings, as amifostine has been shown previously to cause smooth muscle relaxation as a mechanism resulting in hypotension. Noteworthy is the absence of cardiac effects of amifostine. Moreover, cardiotoxicity caused by doxorubicin is known to be induced by free radicals, similar to the mechanism whereby radiotherapy induces cellular lesions. The protective effect of amifostine may be related to its free-radical scavenging activity, similar to the mechanism which applies in radiotherapy.

Maranda, *et al* [Cancer Journal, 1998, Vol.11 (6), p.309-314] reports the use of amifostine with 2-chlorodeoxyadenosine (2-CdA) in mice with L1210 and P388 leukemia. Doses of 20, 35 and 50 mg/kg of 2-CdA were studied in two leukemia cell lines, L1210 and P388. In this study, amifostine (200 mg/kg) apparently reduced the efficacy of the 2-CdA at 50 mg/kg of 2-CdA in the L1210 leukemia and at 35 and 50 mg/kg in the P388 leukemia. No reduced anti-leukemic effect was observed when amifostine was given with 2-CdA at 20 mg/kg. The human dose of 2-CdA (as indicated for hairy cell leukemia) is 90 μg/kg. The relevance of this research study is unclear and the results are unrelated to the current commercial use, or the use of amifostine as proposed in the SNDA.

Bohuslavizki, *et al.*[Strahlentherapie und Oncologie, 1999, Vol 175 (2), p.57-61] This open label randomized pilot study in 17 patients describes the protection of salivary gland function with Ethyol against radioactive iodine and was included as part of the SNDA.

Bohuslavizki, *et al.* [J. Clin Oncol, 1998, Vol 16 (11), p.3542-9] This placebo-controlled study with amifostine and radioactive iodine confirms the results from the previous pilot study and was included as part of the SNDA.

Podolski, *et al.* [Shock, 1998, Vol 10 (6), p.430-5] and Drab, *et al.* [Shock, 1998, vol 10 (6), p.423-9] These two preclinical manuscripts describe the protective effects of

amifostine against LPS induced endothelial cell damage.

Srivastava, *et al.* [Bone Marrow Transplantation, 1999, Vol 23 (5), p.463-467] The authors studied the role of amifostine in the prevention of cyclophosphamide induced hemorrhagic cystitis in rats. On the basis of macroscopic and histologic changes the authors report that animals receiving amifostine showed excellent uro-protection.

Shapiro, *et al.* [Cancer, 1998, Vol 83 (9), p.1980-8] The authors treated 26 consecutive newly diagnosed patients with ovarian cancer with carboplatin 600 mg/m^2 day 1, cyclophosphamide 250 mg/m^2 day 1, and cisplatin 100 mg/m^2 day 8, every four weeks with or without amifostine (range 740-1140 mg/m^2). The authors conclude that although this dose intensive regimen is active, it is also associated with substantial toxicity. In this study, amifostine was well tolerated. An analysis of the first 20 patients entered onto this study revealed no significant difference in moderate to severe toxicities between the treatment arms.

Pawlich, *et al.* [Ginekologia Polska, 1998, Vol 69 (7), p.580-5] Twenty patients with advanced ovarian cancer were treated with cisplatin 100 mg/m^2 and cyclophosphamide 1000 mg/m^2 administered with amifostine. Sixty-five percent of patients had an objective response (35% CR). Tolerance of treatment was satisfactory (one patient discontinued due to side effects). Amifostine markedly decreased chemotherapy toxicity, mainly hematological, and does not appear to negatively influence the efficacy of chemotherapy.

Nici, *et al.* [Cancer, 1998, Vol 83 (9), p.2008-14] The authors studied the role of amifostine against bleomycin induced pulmonary toxicity, which is mediated, at least in part by the generation of active oxygen species. Amifostine significantly decreased the amount of acute lung injury and subsequent fibrosis in this hamster model.

There are some review articles and other small scale clinical studies published in the time frame of this updated literature search which are not further commented on here.

Conclusions

In conclusion, the updated information presented in this Safety Update Report fully supports the conclusions presented in the original SNDA, submitted on December 23, 1998. Based on clinical trial and post-marketing experience, as described in the original SNDA, together with this updated safety report, the draft labeling language (as amended on March 22, 1999) adequately reflects the safety profile of amifostine. In addition, this safety update supports the conclusion that amifostine's use for the proposed indication "to reduce the incidence and severity of radiation-induced xerostomia" is safe.

Update to draft Medical Officer Review for Ethyol

NDA# 20-221 S012
June 2, 1999

The original briefing documents for ODAC from the applicant and from FDA presented different rates for the important primary endpoint of "late xerostomia." After discussion between the Agency and the applicant it became apparent that additional data would have to be submitted to allow an accurate determination of late xerostomia, as that endpoint was defined in the protocol. These data were received June 1, 1999, and the following update gives the FDA analysis, which is similar to the original analysis presented by the applicant.

Results

The protocol-specified analysis included grades 2-4 xerostomia occurring during months 9-12 after therapy. 40% of patients on the RT arm versus 23% of patients on the RT-plus-ethyol arm reported such events (p = 0.0015 by Fishers exact test). FDA also analyzed the number of patients with such reports on both month 9 and month 11 visits. This again favored the ethyol arm (27% versus 13%, p = 0.0031).

	RT alone	RT plus Ethyol	P value
At visit m9 or m11 (primary analysis)	40% (63/158)	23% (36/157)	p = 0.0015
At visit m9 and m11 (exploratory analysis)	27% (42/1578	13% (21/157)	p = 0.0031

In the initial draft review, the agency noted that there was an imbalance in the number of patients receiving higher doses of radiation therapy on the RT-alone arm. The following analysis evaluates whether the Ethyol effect might have been due to this imbalance:

Incidence of late xerostomia according to total dose of radiation therapy

RT dose	Arm: RT	Arm: RT plus Ethyol
<4500	0% (0/5)	0% (0/11)
4501-6500	43% (29/67)	19% (15/81)
>6500	40% (34/86)	32% (21/65)
All doses	40% (63/158)	23% (36/157)

One notes an advantage for the ethyol arm both in the patients receiving mid doses of RT (43% vs. 19%) and for those receiving higher doses (40% vs. 32%), although the advantage is more impressive in the patients receiving moderate doses of RT.

Conclusions Regarding Efficacy

These results suggesting that ethyol decreases grade 2-4 late xerostomia are robust and are clearly statistically significant. The larger effect size noted with these updated data are more persuasive that the observed beneficial effect is real and not due to bias, a phenomenon which could be responsible for smaller effects in a non-blinded trial. As a single trial, several strong signals are noted including improvements in acute severe xerostomia and late grade 2 –4 xerostomia. Signals from salivary production and QOL data are supportive but less impressive. Whether a single trial, unblinded as it was, with these efficacy findings is adequate to support approval is not clear; the question seems ideal for serious consideration by ODAC.

Isagani Mario Chico, MD
Medical Officer

Grant Williams, MD
Medical Team Leader

MEDICAL TEAM LEADER COMMENTS ON NDA

NDA# 20-221/ SE-012
Drug: Ethyol® (amifostine) for Injection

This application seeks approval for Ethyol to "reduce the incidence of severe radiation induced xerostomia. (Severe being defined as ≥RTOG grade 2 acute and late xerostomia)."

Efficacy data come from a single multicenter, randomized, phase 3 trial in patients with head and neck cancer: *WR-0038, Phase III Trial of Radiation Therapy ± Amifostine in Patients with Head and Neck Cancer.* This study compared Ethyol plus standard fractionated radiotherapy (A+RT) with radiotherapy alone (RT) in 303 treated patients. Patient characteristics were generally well balanced on the study arms.

Xerostomia: The primary efficacy endpoints were acute and late xerostomia (grade 2 or higher) and acute mucositis (grade 3). There was no difference between the study arms in the incidence of acute grade 3 mucositis. However acute and late xerostomia (grade 2 or higher) were significantly more common on the RT-alone arm:

INCIDENCE OF XEROSTOMIA, FDA ANALYSES

	RT alone	A + RT	P value
Acute xerostomia	78% (120/153)	51% (75/148)	p < 0.0001
Late xerostomia	40% (63/153)	24% (36/150)	p = 0.0015

FDA and sponsor analyses were quite similar. Slight differences stemmed from use of different groups for evaluation (all treated patients for FDA analyses versus all patients with followup data for Applicant analyses) and from slightly different analysis time windows.

Although FDA noted that more patients on the RT-alone arm than the RT-plus-Ethyol arm received greater than 6500 rads, when patients were grouped according to radiation dose received, a protective advantage for Ethyol was still apparent in each group:

INCIDENCE OF LATE XEROSTOMIA

RT dose	RT alone	A + RT
<4500		0% (0/4)
4501-6500	43% (29/67)	19% (15/81)
>6500	40% (34/86)	32% (21/65)

Furthermore, an evaluation of the overall frequency distribution of dose of RT received showed a similar distribution on the 2 study arms, suggesting that the apparent imbalance was an artifact of the dose cutoffs which were selected.

On June 8, 1999 the advisory committee was asked the following question:

> "Does this trial provided substantial evidence that Ethyol decreases the incidence of moderate-to-severe xerostomia in patients undergoing radiation treatment for head and neck cancer?"

The committee had a long discussion that included criticisms such as:

- the assessments were not blinded, and
- the SWOG criteria were not quantified.

However, the radiotherapists on the committee felt that it was relatively easy for physicians treating such patients to determine the difference between grade I and grade II xerostomia. The committee voted in the affirmative (11 to 2) on this question.

Salivary Measurements: Evaluation of salivary production was a secondary endpoint. Clinically meaningful levels of saliva production and time categories for saliva collection analysis were defined retrospectively. In the analysis of unstimulated saliva collection, the applicant used > 0.1 gram of saliva as the cutoff of adequate function, used the time window of one year's follow-up (defined as 6 to 15 months after treatment), and noted a significant difference in favor of the Ethyol arm (63 patients with adequate function on the Ethyol arm versus 43 patients on the RT arm,$p = 0.003$). The analysis of stimulated saliva collections by the applicant and longitudinal analysis of unstimulated saliva collections by the FDA did not show statistically significant differences between study arms. The advisory committee was asked the following question:

> "Do the results of the salivary measurements provide supportive evidence that Ethyol reduces the incidence and severity of late xerostomia?"

Again, after a discussion of criticisms, including the fact that the specifics of the analysis were retrospectively detailed, the committee voted in the affirmative (12 to 1) to this question.

Patient Benefit Questionnaire (PBQ): As described in Dr. Chico's review, analytical plans for this parameter were submitted retrospectively. Consequently, the applicant and the Agency chose different methods of analysis. The applicant evaluated the overall mean of the 7 subscales of the PBQ and found statistically significant differences in favor of Ethyol 7 months ($p=0.009$) and 1 year ($p=0.008$) after completion of therapy. The longitudinal analyses by the FDA looked at three discrete areas identified by the reviewers as most clinically significant (functional well being, global assessment of dryness and use of external aids) and found trends in favor of Ethyol. The committee was asked the following question:

"Do the results of the patient benefit questionnaire provide support to this application?"

During discussion of this matter before the committee, the Applicant stated that the PBQ questionnaire had been used in other trials of head and neck cancer, but the Applicant did not know of any publications which described such result. Again, despite a thorough and critical discussion, the committee felt that these data were supportive, voting in the affirmative (11 to 1) to this question.

Tumor Control: In the evaluation of cytoprotective agents such as Ethyol, one must consider the adequacy of evidence demonstrating that the cytoprotective agent is not protecting the tumor from anticancer treatment. In this case, the FDA determined that relatively large trials in patients with head and neck cancer would be needed to rule out such a tumor protective effect relative to radiation therapy. The most relevant data submitted is from the randomized controlled study discussed above. In this trial no difference was noted between the arms in time to locoregional [RT:A+RT 0.95 (0.64, 1.39], disease free survival [0.99 (0.69, 1.42)] and overall survival [1.35 (0.87, 2.1)]. The lower bound of the 95% confidence intervals cannot exclude the possibility that Ethyol is 36%, 31%, and 13% infererior, respectively. The sponsor also cited data from a 100-patient randomized study of Radiation Therapy +/- Ethyol in rectal cancer and data from a randomized trial of chemotherpay +/- Ethyol in ovarian cancer. The committee was asked the following question:

"Is there adequate evidence that Ethyol does not protect tumors during treatment of head and neck cancer with radiation therapy?"

The committee's deliberation on this issue was most useful. Dr. Harwood, one of the radiotherapists on the committee, noted that about two thirds of the patients in the trial had received RT in the post-operative setting. He felt that for this group of patients, who tend to recur earlier, the numbers of patients evaluated in the randomized study and the length of follow-up were sufficient. He stated that patients who receive definitive radiation therapy for head and neck cancer, however, tend to recur later, and that there were too few patients followed up for too short a time in the randomized study. The committee agreed, and amended the indication in the above question to include only patients being treated with post-operative radiotherapy for head and neck cancer. The committee voted in the affirmative (9 to 2) to the question so amended.

Safety Profile: There were significantly more severe adverse and more hospitalizations in the A+RT arm. Adverse events attributed to Ethyol are listed in the following table:

Incidence of Treatment-Related Adverse Events Associated With Amifostine

Adverse Experience	A+RT (N=150) n	(%)	RT (N=153) n	(%)	P value
Nausea	66	(44%)	25	(16%)	**<0.0001**
Vomiting	55	(37%)	11	(7%)	**<0.0001**
Hypotension	22	(15%)	2	(1%)	**<0.0001**
Fever	12	(8%)	3	(2%)	**0.0174**
Allergic reaction	8	(5%)	0	—	**0.0033**
Dizziness/Lightheadedness	7	(5%)	0	—	**0.0068**

Approvability:

A critical issue for the approvability of this application was whether one randomized study would suffice. The committee's opinion on the strength of evidence, the reliability, and the clinical relevance of the findings in this study were critical to this FDA judgement. Therefore, in the preamble to the final question to the committee, the FDA stated the criteria needed to find the application approvable under these circumstances:

> "Regulations require that substantial evidence of effectiveness be demonstrated through adequate and well-controlled investigations. In most cases, the FDA has required more than a single trial. As noted in the 1998 FDA Guidance for Industry, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products,* "In other cases, FDA has relied on only a single adequate and well-controlled efficacy study to support approval—generally only in cases in which a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study would have been difficult to conduct on ethical grounds."

The FDA clarified that body of the guidance document stated the irreversible morbidity was one of the important clinical benefits upon which a judgement could be based. The committee was asked the following question:

> "Considering the efficacy evidence presented from this single randomized phase 3 study, considering the safety data, and considering the data on tumor protection, should Ethyol be approved "to decrease the incidence of moderate-to-severe xerostomia in patients undergoing radiation treatment for head and neck cancer?"

Again the committee modified the indication to "post-operative radiotherapy," and voted in the affirmative (9 to 2).

At the time these findings were presented to the Oncologic Drugs Advisory Committee, the review team considered evidence supporting the application borderline because of concerns in two areas:

-The application submitted data on only one trial demonstrating efficacy.
-The largest study had limited power to exclude a tumor-protective effect.

It was critical that the Agency obtain input from ODAC on the acceptability of these data in this clinical setting. With a clear understanding of the limitations of the data, ODAC, in near unanimous votes, declared that the xerostomia findings were substantial evidence of efficacy, and that the data on saliva production and data from patient questionnaires were supportive. After evaluating the requirements outlined in the Agency's guideline on providing evidence of efficacy, including the limited circumstances under which a drug might be approved with only a single clinical trial, the committee recommended that the application be approved. The committee heard the Agency's concern regarding tumor protection, and made a reasonable recommendation that the indication be limited to patients receiving post-operative radiotherapy.

Conclusion and Recommendation

The size and statistical significance of the decrease in xerostomia associated with Ethyol treatment and the presence of other supportive data (whether or not one determines the findings to be statistically significant) are convincing even in an unblinded trial. There is no evidence of tumor protection in a trial of moderate size. I agree with the recommendation of ODAC that Ethyol should be approved to decrease the incidence of moderate to severe xerostomia in patients receiving post-operative radiotherapy for head and neck cancer.

/S/ 6/22/94

Grant Williams, MD
Team Leader
Division of Oncology Drug Products

ABSTRACT

Radiation can often lead to temporary or permanent damage to normal tissues. Acute xerostomia is a particularly bothersome symptom to patients; however, later radiation toxicities are often permanent and have profound effects on the patient's long-term health and well being. NDA application 20-221 seeks approval for treatment with Ethyol ® for reduction of the incidence and severity of radiation-induced xerostomia. Data from 303 patients in a Phase 3 randomized, multicenter study supported by study reports from three studies with approximately 200 patients were presented.

The objectives of the phase 3 study were to determine if the addition of Ethyol® to standard fractionated radiotherapy reduced the incidence of oral radiation toxicities without decreasing antitumor efficacy. Patients with squamous cell carcinoma were stratified according to site of disease, nodal status, Karnofsky Performance Status, percent of the parotid glands in the radiation fields, and type of radiation. Each was randomized to receive RT (1.8 to 2.0 Gy 5 days/week for 6-7 weeks) ± Ethyol® (200 mg/m^2 i.v. prior to RT). Primary efficacy endpoints related to radiation effects include the reduction of grade 2-4 acute and late xerostomia, and grade 3-4 acute mucositis; and locoregional tumor control at one year. Secondary endpoints include measurement of whole saliva production and parotid saliva production, time to onset and duration of xerostomia and mucositis, patient benefit analysis through a patient benefit questionnaire (PBQ), disease free survival and overall survival. A total of 315 patients were randomized, with 150 patients in the amifostine + radiotherapy arm (A+RT) and 153 patients in the radiotherapy only (RT) arm included in the intent to treat analysis.

Pretreatment patient characteristics were balanced. Using the intent to treat analysis, the incidences of moderate to severe (≥Grade 2) acute (A+RT: 51% vs. RT: 78%, p<0.0001) and late (A+RT: 24% vs RT: 40%, p=0.0015) xerostomia were significantly reduced in the A+RT arm. There was no significant difference in acute mucositis (A+RT: 35% vs RT: 39%, p=0.48) and overall incidence of acute (A+RT: 94% vs. RT: 90%, p=0.07) and late (A+RT 30% vs RT: 36%) xerostomia (Grade 1+ Grade 2). Unstimulated saliva collections showed a significant advantage for Ethyol®at the one year follow-up analysis (A+RT: 72% vs RT: 49%, p=o.003). This was not confirmed by data from stimulated saliva collections (A+RT: 33% vs. RT: 41%, p=0.35) and the FDA analysis using comparisons with mean baseline measurements. The analysis plan for the patient benefit questionnaire was determined retrospectively and the applicant and the FDA chose different methods of analyses. The applicant found statistically significant differences between treatment arms in favor of Ethyol® at seven months (p=0.009) and one year (p=0.008) after completion of therapy in the overall mean scores of seven subscales of the PBQ. The FDA longitudinal analysis looked at three discrete areas identified by the reviewers as most clinically significant (functional well-being, global assessment of dryness and use of external aids). These analyses only found trends in favor of Ethyol® but did not yield significant findings.

There was no difference noted between the treatment arms in time to locoregional failure [RT:A+RT 0.95 (0.64,1.39)], disease free survival [0.99 (0.69,1.420] and overall survival [1.3590.87,2.10]. However, the lower bound of the 95% confidence intervals cannot exclude the possibility that Ethyol® is 36%, 31% and 13% inferior, respectively. Data from a randomized study of RT ± Ethyol® in rectal cancer and data from a randomized trial of chemotherapy ±

Ethyol® in ovarian cancer were also cited. During the advisory committee deliberations, the proposed indication was amended to include only patients being treated with post-operative radiotherapy. A minority of patients received definitive radiotherapy in the trial and since they tend to recur later, it was felt that there were too few patients and that their follow-up was too short.

Monitoring of adverse events showed expected but significantly higher incidences of nausea, vomiting, hypotension, fever, allergic reaction, dizziness and lightheadedness despite lower daily doses of Ethyol® . Seventeen percent of patients discontinued Ethyol® due to adverse events; however, all but one patient continued to receive full radiation therapy. There were more skipped treatments and more hospitalizations due to adverse events in the Ethyol® arm.

With a clear understanding of the limitations of the data, the Oncologic Drugs Advisory Committee declared that the findings regarding xerostomia were substantial evidence of efficacy, and that the data on saliva production and data from patient questionnaires were supportive. After evaluating the requirements outlined in the Agency's guideline on providing evidence of efficacy, including the limited circumstances under which a drug might be approved with only a single trial, the committee recommended that the application be approved. The committee heard the Agency's concern regarding tumor protection, and recommended that the indication be limited to patients having post-operative radiotherapy. Approval of sNDA 20-221 SE102 for the use of Ethyol® to "decrease the incidence of moderate to severe xerostomia in patients receiving post-operative radiotherapy for head and neck cancer" is recommended.

SUMMARY OF BENEFITS, RISKS AND CONCERNS

BENEFITS/ STRENGTHS	RISKS/ WEAKNESSES	CONCERNS/ UNCERTAINTIES
Study Design and Conduct • Large, randomized Phase 3 • Well-balanced population with respect to disease stage, parotid gland exposure, KPS and type of radiation • Usual daily fractionated RT dose given • RT Quality Assurance Team • DSI inspection OK	• Retrospective definition of efficacy analyses: - clinically meaningful levels of saliva production and time categories for saliva collection analysis • Small sample numbers for parotid saliva collection and scintigraphy analysis • Time to event analyses lack robustness due to few events at one year follow-up	• Should the trial have been placebo controlled? • Is one trial adequate? • Potential effect of large amifostine drop outs on efficacy endpoints • Is the data ruling out tumor protection adequate?
Efficacy • Significantly reduced ≥Gr2 acute xerostomia • Higher median cumulative RT dose before onset of ≥ Gr 2 acute xerostomia • Significant reduction in incidence of ≥Gr 2 late xerostomia • Significant difference in unstimulated saliva at one year using categorical cut-off identified by expert as clinically relevant. • PBQ: Trend towards better change from baseline, significant at end of treatment and one year follow-up. Significant difference in "general condition" among drop-outs • No difference in median survival among patients with rectal CA (supporting study)	• Patients in RT group received significantly higher total doses of radiation • No difference in overall incidence of acute and late xerostomia • No difference in stimulated saliva production • PBQ: Significant attrition/missing data, No difference in functional well-being and use of external aids • Weak evidence against tumor protection	
Safety	• 29 of 150 patients (19%) discontinued amifostine due to adverse events • Significantly greater frequency of known adverse events • More radiotherapy doses missed in the A+RT • More hospitalizations	