

## OPINION:

# The opinion of Hungarian Association of Oral and Maxillofacial Surgeons (*Magyar Arc-, Állcsont- és Szájsebészeti Társaság*) on the justification of supportive treatment of patients with tumorous diseases of the oral cavity

The Hungarian Association of Oral and Maxillofacial Surgeons (*Magyar Arc-, Állcsont- és Szájsebészeti Társaság*) has reviewed the research results related to Avemar and issued its opinion as follows:

For patients suffering from head- and neck tumors - primarily malignant tumorous diseases of the oral cavity, the progression of the disease can be slowed significantly, the five-year survival rate increased considerably, the quality of life improved, and the oxidative stress on the patients reduced by the long-term application of the supplementary formula Avemar. The Association considers the supportive treatment with the formula Avemar as an important part of the complex therapeutic protocols applied in stages II, III and IV of malignant tumorous diseases of the oral cavity.

### Reasoning

### History

The preparation called Avemar, developed by Hungarian researchers, has been registered by the National Food and Nutrition Science Institution (*Országos Élelmezés- és Táplálkozástudományi Intézet*) in the category "special therapeutic purpose formula for patients with tumorous disease" (Registry No: 503; OÉTI 6157/2001); its marketing has been authorized by the National Officer of Pharmacist General (*Országos Tisztai Főgyógyyszerész*), OTH/97-46/2002, by notice of the Ministry of Health (*Egészségügyi Minisztérium*), Health Bulletin (*Egészségügyi Közlöny*) July 1, 2002. Avemar is manufactured utilizing GMP (Good Manufacturing Practice), under supervision of the National Pharmaceutical Institution (*Országos Gyógyszerészeti Intézet*), OGYI/1 127-100/38/2003.

According to available documentation and peer-reviewed publications, Avemar has not shown toxic effects either in acute, sub acute, or chronic toxicological tests. In controlled human studies, Avemar did not have any adverse effects after either 1, 3, or 5 years of application. The preparation has not shown any adverse

interaction with cytostatics, hormone formulations and immunological drugs. In the USA, Fermented Wheat Germ Extract (FWGE), the generic description of Avemar, has been affirmed as GRAS (Generally Recognized As Safe) in accordance with Food & Drug Administration procedures, a certification of the safety of food ingredients.

Studies have been conducted both in Hungary and abroad to explore the effects of Avemar. The favorable clinical effects of the formula can be contributed to the induction of apoptosis, the inhibition of transketolase, ribonucleotide-reductase, several types of kinase and the cyclooxygenases, the activation of natural killer cells, as well as the induction of the intracellular adhesion molecule (CD54, ICAM-1) expression. Clinical studies with the supportive application of Avemar have been conducted in patients suffering from colorectal cancer, malignant melanoma, lung cancer, pediatric solid tumorous diseases, and head and neck cancers. The results have been published in recognized journals; 18 publications can be found in the Medline database.

### The supportive application of the formula in the complex treatment of tumors of the oral cavity

Three clinical studies have been conducted with Avemar in the supportive treatment of head-, cervical- and oral cavity cancers.

#### *Ear, Nose and Throat Clinic of Semmelweis University*

Based on The Scientific and Research Ethics Committee (ETT-TUKEB) Authorization number 9-3/1998, the open, observation-based clinical study of Avemar as supportive care in the treatment of patients suffering from head and neck tumors was started in January, 1999 at the Ear, Nose and Throat Clinic of Semmelweis University, under the direction of Professor Ottó Ribári.

Fifty patients, primarily with tumors of the larynx- and the pharynx, were included in the study. Patients with tumors of the bone, salivary gland and other soft tissues were also included in the study in a small number. The histological diagnosis was squamous cell carcinoma in

80% of the cases. Avemar was consumed daily as a part of the complex oncological treatment, both concurrently and after the surgery, as well as during radio- and chemotherapy. At the end of the three-year-long study it was established that majority of patients taking Avemar experienced no tumor recurrences or metastasis after surgery and radiation, and/or chemotherapy. In some of the patients even the existing recurrences and metastasis regressed. Avemar increased the therapeutic effects of both chemo- and radio-therapy, while significantly reducing the side effects. The appetite of patients taking Avemar improved, and the body weight of cachectic patients increased. They regained their general condition and physical strength (Quality of Life). No side effects were observed in relationship with the application of the formula. In the case of six patients with very advanced malignant tumor of the salivary gland, the application of the formula was started after the surgery and irradiation. After three years, the absence of tumor and metastasis was observed with 5 patients. The advanced tumor of the salivary gland of the sixth patient had already caused a neck metastasis; the patient had undergone surgery and full-dose irradiation treatment. Every sixth week a cytostatic treatment was applied until the end of the cycle, with the concurrent application of Avemar. The further cytostatic treatment was suspended – while applying the formula only – for more than half a year, but no progression was observed despite of this, moreover, the physical strength of the patient had significantly increased and his/her body weight had increased by 5 kg. In an identical clinical arrangement, the above effect had been also observed in the case of three patients with malignant bone- and soft tissue tumors. Professor Ottó Ribári, in the summary of his report dated April 16, 2003, submitted to the Chairman of The Scientific and Research Ethics Committee (ETT-TUKEB), emphasizes that “Avemar is a very effective supportive formulation in the treatment of tumors. The formulation is recommended, not as a replacement for surgery or irradiation treatment, but as a supportive application concurrent with the clinical treatments, as well as an independent application after their completion.”

#### **Oral Surgery and Dental Clinic of Semmelweis University**

Based on the The Scientific and Research Ethics Committee (ETT-TUKEB) Authorization number 186/1999, professor György Szabó and his colleagues, Márta Ujpál and Emese Fülöp, of Oral Surgery and Dental Clinic of Semmelweis University, conducted a comparative clinical study, which investigated the Avemar-treatment in the supportive therapy of tumors of the oral cavity. Consecutive patients of age between 18 and 80 years participated in the study, with a diagnosis of no more than 3 months, suffering from malignant tumorous disease of the oral cavity, in stages UICC II and

III according to the TNM-system. The objective of the study was to determine whether the continuous application of Avemar for one year has any effect on the process of stage II and III tumorous disease of the oral cavity, otherwise being treated *lege artis*. (state of the Art). The patients had undergone radical surgeries, and some of them received adjuvant chemotherapy (cisplatin, methotrexate, Bleocin combination) and irradiation treatment (irradiation with dose of 60 Gy). Furthermore, patients in the Avemar group took one dose of Avemar (8.5g Avemar pulvis) per day, suspended 150 ml cold drinking water. The formulation was taken 1 hour before one of the main meals. 45 patients participated in the study; 23 persons (9 males and 14 females) in the Avemar group, and 22 persons (14 males and 8 females) in the control group. There was no statistically significant difference in the ratio of the sexes. The average age of the patients was 55.4 years (29-80 years) in the Avemar group and 62.4 years (41–77 years) in the control group. There was no statistically significant difference in the age distribution between the two groups, either. The distribution by stage is listed in *Table 1*.

Table 1: Distribution of tumors by stage at the time of entering in the study

UICC stage	AVEMAR group		Control group	
	cases	%	cases	%
II.	11	47.8	11	50.0
III.	12	52.2	11	50.0
Total	23	100.0	22	100.0

There was no statistically significant difference in the distribution of stages between the Avemar group and the control group (Mann-Whitney-trial:  $z = 0.131$ ;  $p = 0.896$  N.S.).

The distribution of tumors according to the place of origin (anatomical region): tongue - Avemar: 6, control: 6; gingiva - Avemar: 8, control: 5; oral foundation - Avemar: 6, control: 7; other - Avemar: 3, control: 4. By histology testing: 44 squamous cell carcinoma and 1 adenocarcinoma.

Recurrences at the beginning of the study (at recruitment): Avemar group: 4/23 (17.4%); control group: 0/22 (0.0%). There was no significant difference between the two groups, but the prognosis of the Avemar group can be considered worse (Fisher exact test:  $p = 0.059$ , at the borderline of significance.)

Received chemotherapy: Avemar group: 6/23, that is 26.1%; control group: 6/22, that is 27.3%. There was no significant difference between the two groups ( $p = 0.597$ ).

Received radiotherapy: Avemar group: 3/23, that is 13.0%; control group: 9/22, that is 40.9%. There was a significant difference between the two groups, to the disadvantage of the Avemar group (Fisher exact test:  $p < 0.05$ ). The results of the end-point analysis after one year are shown in *Table 2*.

**Table 2:** End-point analysis after 1 year

	Avemar group	Control group	Comparison of the treated and control group *
Case number	23	22	-
Death	0	1	N.S.
	0.0%	4.5%	
Local recurrences	1 case 4.3%	12 cases 54.5%	p <0.001
New metastasis	1 case 4.3%	4 cases 22.7%	N.S.
Progression event (case)	2 cases 8.7%	17 cases 77.3%	p <0.001
Progression event (person)	2 persons 8.7%	13 59.1%	p <0.001

\*Fisher exact test

No side effects were experienced during the application of the formula

It had been established that, the continuous application of the formula for 1 year had significantly decreased (by almost one order of magnitude) the progression of diseases (characteristically to the stage of the disease, mainly the recurrences) of patients suffering from stage II and III tumorous diseases of the oral cavity, who had undergone radical surgery and received adjuvant chemotherapy and irradiation treatment as needed. Calculation of the relative risk of progression:

$$\text{risk} = \frac{\text{Incidence Avemar}}{\text{(Control)}} = \frac{0.0869}{0.591} = 0.147 \text{ Incidence}$$

Relative risk reduction (RRR) = 1 – RR = 1.000 – 0.147 = 0.853 (85.3%), that is, the Avemar treatment a had reduced the risk of progression events by 85.3%.

Absolute risk reduction (ARR) = Incidence (control) – Incidence (Avemar) = ARR = 0.591 – 0.0569 = 0.534.

$$\text{Number needed to treat (NTT) for preventing an event} = \frac{1}{\text{ARR}} = \frac{1}{0.534} = 2.0$$

that is, the Avemar treatment of 2 patients for 1 year is needed so that for 1 patient the progression events can be prevented.

The total survival rate of the patients was studied by a five-year follow-up. After five years, 17 patients were alive from the Avemar group (74%), and 10 patients were alive from the control group (45.5%). The difference significance (z- and ÷2-trial: p <0.05).

The investigators established that by the long-term application of the supplemental Avemar formula in

malignant tumorous diseases of the oral cavity the ratio of local reoccurrences can be significantly decreased and the five-year survival rate can be significantly increased. The investigators suggested that the complex therapeutic protocols applied for malignant tumorous diseases of the oral cavity be supplemented by the supportive treatment with the formula Avemar.

### *Multicenter study in Italy*

In an open, controlled, multicenter study in 5 centers in Italy (Azienda Ospedaliera Universitaria San Martino, Genova, Ospedale Evangelico, Torino, Ospedale di Lecco, Lecco, ASL1, Carrara, Ospedale di Montecchio Maggiore, Montecchio Maggiore, Vicenza) the effect of supplemental Avemar formula, administered for 60 days, on the quality of life and oxidative stress of patients with advanced (stage III-IV) head-neck tumors. 55 patients who had undergone surgery participated in the study (Avemar: 22, control: 33). There was no difference between the two groups in the distribution of age and sex as well as the frequency of radio-chemotherapy and enteral feeding treatments, except the preventive irradiation treatment, which the patients in the control group received in a larger proportion.

At the end of the study, the body mass index (BMI) of the patients in the Avemar group had not changed, while that of the patients in the control group had decreased significantly.

No side effects were experienced in relationship with the application of Avemar.

The oxidative stress load (the level of hydroperoxides in the circulation) had significantly decreased by the application of Avemar.

At the start there was no difference between the quality of life (Spitzer QOL index) of the patients of the two groups, while at the end of the 60-day study the quality of life of the patients receiving Avemar treatment was significantly better than that of the control patients (Mann-Whitney U-test, p = 0.0444).

The investigators established that the supplemental Avemar-treatment is safe on the one hand, and it is of key importance (“pivotal”) in the complex treatment of patients with advanced or terminal stage head-neck tumors.

Note: The opinion has been unanimously accepted at the board meeting of Magyar Arc-, Állcsont- és Szájsebészeti Társaság (Hungarian Face-, Maxillary- and Dental Surgical Association) held on October 20, 2005.

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*Dr. József Barabás*  
university professor  
Chairman of Magyar Arc-,  
Állcsont és Szájsebészeti Társaság

*Dr. Zsolt Németh*  
university adjunct  
Secretary of Magyar Arc-,  
Állcsont és Szájsebészeti Társaság