

The Pain of Oral Mucositis

a report by

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The Scope of the Problem

Over the past two decades, advances in the supportive care of oncology patients have permitted more aggressive treatment strategies that would otherwise not have been possible. However, the prevention and treatment of oral mucositis (OM) remains a dilemma. The American Cancer Society in 1999 estimated that approximately 400,000 patients annually will experience some type of oral complication as a result of their cancer treatment.¹ The tissue trauma and associated pain of OM were identified as major clinical problems as far back as the 1970s, yet they remain a significant concern for the majority of patients undergoing cancer treatments.² The National Cancer Institute estimated in 2005 that almost 100% of patients receiving radiation therapy for head and neck cancers experience OM, as do 80% of patients undergoing hematopoietic stem cell transplantation and 40% of patients receiving standard-dose chemotherapy.³ Most patients who have experienced OM report that it is the most bothersome side effect of their cancer treatment. OM is a multifaceted problem that can lead to a number of clinical complications. It can manifest itself in various ways, but pain is the hallmark symptom and may be the first indication that OM is developing. The inability to eat and drink can lead to problems with maintaining nutrition and subsequent weight loss. It may be necessary for patients to have a feeding tube placed to ensure adequate nutrition. Pain can significantly impact a patient's quality of life and trigger a cluster of symptoms including fatigue and depression. OM is a dose-limiting side effect that may result in treatment delays, dose reductions, or the

stopping of treatment altogether. It is essential to have strategies in place to manage the pain associated with OM.

Mucositis Survey

Recently, a survey enquiring about several aspects of OM was conducted at the 32nd Annual Oncology Nursing Society (ONS) Congress, which was held April 24–27, 2007 in Las Vegas, Nevada. Respondents were asked to rank the significance of OM in their clinical setting and against other supportive care issues; indicate if they had specific guidelines for the management of OM; and list first- and second-line OM pain management interventions and rate their effectiveness. A five-point Likert scale was used, with responses from 'not important' to 'very important.' Not surprisingly, 89% of the 558 respondents identified OM as a significant problem. Pain was the primary issue identified by 93% of the respondents as 'most important' to their patients, followed by pain on swallowing (87%) and difficulty speaking (73%). Nurses ranked OM very high (92%) relative to other supportive care issues faced by cancer patients. Nurses were overwhelmingly identified (81%) as the healthcare professionals responsible for the initial evaluation and management of OM in their practice setting. Fifty-seven percent of respondents reported that they did not have specific institutional guidelines in place for the management of OM. The survey revealed myriad products used as first- and second-line agents in the management of OM pain (see *Table 1*). The multi-agent rinse 'magic mouthwash' (pharmacy compounded), oral pain medications, and sucralfate were the primary management strategies used in an attempt to alleviate the pain caused by OM. The effectiveness of these first-line agents in relieving the pain of OM was dismal, with 67% of the respondents rating them as only minimally effective. These survey results are not surprising. They reinforce the fact that OM remains a significant clinical problem that is currently being treated with ineffective agents. Many nurses still do not have specific clinical guidelines to assist them in the management of OM.

Pathophysiology

Historically, OM was thought to arise solely as a consequence of epithelial injury. Both chemotherapy and radiation therapy were believed to target non-specifically the rapidly proliferating cells of the basal epithelium, causing a direct inhibitory effect on DNA replication and mucosal cell proliferation. This inhibition, it was hypothesized, led to a reduced renewal capability of the basal epithelium resulting in atrophy, collagen breakdown, and eventual ulceration. Furthermore, it was believed that the process was facilitated by trauma and the entry of oral micro-organisms. However, recent clinical investigations have shown that submucosal damage actually precedes the appearance of epithelial lesions by as much as one week.⁴ Originally, OM was thought to be a four-phase process consisting of an initial inflammatory phase, an epithelial phase, an ulceration phase, and, finally, a



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healing phase. Sonis et al.⁵ proposed a five-phase model for the pathobiology of OM. Phase I, 'initiation,' occurs when radiation therapy and/or chemotherapy cause damage to the DNA in the basal epithelium, leading to the release of reactive oxygen species (ROS), which are normally a natural by-product of oxygen metabolism and have an important role in cell signaling. However, during times of stress ROS levels can increase dramatically, which can result in cell damage. In the case of OM, the ROS surge leads to further trauma to the cells and blood vessels in the submucosa. At this stage, the mucosa still appears normal on examination, although all the events that ultimately lead to ulceration have already been triggered. Denham and Hauer-Jensen⁶ reported that, although there is death of some cells within the basal and suprabasal epithelium at this point, it is the destruction of the cells in the underlying submucosa that makes the largest contribution to injury.

Phase II, 'signaling,' begins when the ROS induce apoptosis, or programmed cell death, and generate a complex series of events. DNA strand breaks result in the activation of several transduction pathways that activate factors such as p53 and nuclear factor- κ B (NF- κ B). NF- κ B is significant because it results in the upregulation of up to 200 genes, many of which potentially have an effect on mucosal toxicity. The upregulation of these genes results in the production of large quantities of cytokines, including tumor necrosis factor- α (TNF- α), interleukin (IL)-1 β , and IL-6. These damage the connective tissue and endothelium, ultimately resulting in epithelial basal cell injury and death. Fibroblasts are also targeted in this phase, as the activation of metalloproteinases (MMPs) leads to the destruction of the collagenous subepithelial matrix and the breakdown of the epithelial basement membrane. Some of the cytokines released in phase II not only damage tissue directly, but also provide a positive feedback loop that compounds the injury. This is phase III, 'amplification.' For example, the TNF- α that is released also activates NF- κ B, as does IL-1 β . Even at this stage, although there may be some mucosal erythema, tissue integrity remains intact and patients usually have few symptoms.

Eventually, epithelial integrity breaks down and painful ulcerations develop, allowing bacterial entry. This is phase IV, 'ulceration.' The colonizing bacteria further increase injury by shedding cell wall products, which penetrate into the submucosa, releasing even more cytokines. This is particularly worrisome in neutropenic patients, as the introduction of numerous micro-organisms increases the risk of systemic infection. OM is most often an acute phenomenon that may resolve spontaneously once cancer therapy ends. Phase V, 'healing,' begins when cells from the extracellular matrix send messages that induce the epithelial cells to divide and start the process of mucosal renewal. Both treatment-related and patient-related factors play an important role in the development of OM. The type of cancer treatment (radiation versus chemotherapy), the agents selected, and the dose and timing of therapy are all treatment-related factors that impact the extent and severity of OM. Some chemotherapeutic agents, such as methotrexate and etoposide, can be found in salivary fluid and, therefore, have a direct toxic effect on the epithelium. Age, poor renal function, prolonged exposure to steroids, and poor oral hygiene also contribute to the development of OM.

Literature Review

Unfortunately, OM is an inevitable, costly, and debilitating consequence of cancer therapy. Historical approaches to treatment focused solely on palliation, with the objective of helping the patient to tolerate symptoms and control infection. Although palliation is still an important goal, greater focus

Table 1: Oncology Nursing Society Oral Mucositis Survey Data

Mucositis Pain Interventions	First-line (%)	Second-line (%)
Magic mouthwash	77	7
Sucralfate (Carafate®)	22	20
Fluoride rinses	8	9
Barrier agents (Gelclair®)	17	11
Electrolyte rinses (Caphosol®)	3	8
Pain medication (oral)	37	24
Pain medication (parenteral)	16	17
Other (please specify)	10	2

Data from the ONS 32nd Annual Conference; n=558.

Table 2: Scoring Systems/Assessment Tools for Oral Mucositis

Title	Measures
World Health Organization (WHO)	Oral mucosa appearance and difficulty swallowing
National Cancer Institute Common Toxicity Criteria (NCI-CTC)	Oral mucosa appearance only; standardizes adverse events in clinical research trials
Oral Mucositis Scale (OMAS)	Records anatomical distribution of oral lesions; no functional assessment
Oral Assessment Guide (OAG)	Anatomical and functional assessment

on the pathogenesis of OM has generated interest in developing a successful intervention. However, despite numerous clinical studies and multiple reviews addressing many preventive and treatment modalities, the management of OM remains an unsolved problem. One consistent theme throughout the literature is the importance of oral care in OM prevention and the effective management of the associated pain. Pre-treatment assessment with dental evaluation and dental procedures performed at least three weeks before the beginning of toxic therapy have been shown to reduce the incidence and duration of OM. Patients with an intensive dental care protocol developed fewer painful oral complications compared with those who received limited dental care. Regrettably, the pain of OM is rarely addressed in the literature despite its widespread occurrence. However, one study published in the *International Journal of Oncology, Biology and Physics* in 1992⁷ reported that a well-defined regimen for mouth care and analgesic administration resulted in improved management of radiation-related mucositis compared with inconsistent nursing intervention and the absence of an analgesic protocol.

A host of agents has been investigated for the treatment and/or prevention of OM in cancer patients, most often including the use of antimicrobials, anti-inflammatory agents, and granulocyte-macrophage colony-stimulating factors. The quality of published papers is variable and no intervention has been unequivocally shown to be effective. The notable lack of a standardized scoring system for OM has hampered high-quality research in this field. Several scoring systems have been devised, such as the World Health Organization (WHO) scale,⁸ the National Cancer Institute Common Toxicity Criteria (NCI-CTC),⁹ the Oral Mucositis Assessment Scale,¹⁰ and the Oral Assessment Guide.¹¹ Each of these systems is useful in select situations, but no one scale has gained widespread acceptance for clinical application (see *Table 2*). Keratinocyte growth factor (KGF) has become popular in the literature and in 2004 the US Food and Drug Administration (FDA) approved the first active KGF agent, palifermin, for the prevention and treatment of OM. Several studies cite the benefit of KGF in the stem cell transplant setting, but ongoing trials need to evaluate further the ability of palifermin to reduce OM in patients receiving radiochemotherapy for head and neck cancer.¹²⁻¹⁵

Table 3: Updated Clinical Practice Guidelines for the Prevention and Treatment of Oral Mucositis

Not Recommended for Use	
Chlorhexidine	Acyclovir and its analogues
Antimicrobial lozenges	Pentoxifylline
Sucralfate	GM-CSF mouthwashes
Compounded mouthwashes	

Source: Keefe et al., 2007.¹⁹

Coating agents are also commonly cited, with most research evaluating sucralfate and ‘magic mouthwash.’ Kostler and colleagues reviewed eight studies published between 1988 and 2000 that investigated the efficacy of sucralfate rinses in radiation patients.¹⁶ They concluded that sucralfate seems to have little, if any, benefit compared with standard oral hygiene and symptomatic treatment of OM. A clinical study comparing pain relief and overall pain scores associated with salt and bicarbonate alone, chlorhexidine, and magic mouthwash with lidocaine, diphenhydramine, and Maalox® was conducted by Dodd et al.¹⁷ There was no difference in the severity or duration of OM among any of the three arms. Gelclair®, a newer barrier agent, has shown promise in decreasing pain resulting from mucositis, aphthous ulcers, and oral surgery.¹⁸ In 2007, the Multinational Association of Supportive Care in Cancer and the International Society for Oral Oncology (MASCC/ISOO) updated their clinical practice guidelines for the prevention and treatment of mucositis.¹⁹ This update was prompted by advances in the field of mucositis over the past three years, published literature between January 2002 and May 2005, and a consensus view based on the criteria of the American Society of Clinical Oncology. Palifermin was recommended for the prevention of OM associated with stem cell transplant, amifostine for radiation proctitis, and the addition of cryotherapy for mucositis associated with high-dose melphalan. Sucralfate and antimicrobial lozenges were not recommended for radiation-induced oral mucositis (see *Table 3*).

Risk Factors

OM is influenced by a variety of patient- and treatment-related risk factors. Patient-related factors include age, female gender, prior occurrences of herpes and OM, diabetes, tobacco and alcohol use, periodontal disease, poor nutrition, medications, and immune suppression. Younger patients and the elderly are most at risk for the development of OM. Tobacco and alcohol exacerbate periodontal disease and irritate the oral mucosa. Xerostomia prior to treatment may impair the permeability of the oral mucosa and reduces the pH of the saliva, resulting in tooth decay and gingivitis. Malnutrition can lead to increased dental decay, contribute to dehydration, and delay the healing of the oral mucosa. Medications that contribute to xerostomia may actually promote periodontal disease and predispose the oral cavity to bacterial and fungal overgrowth. Weekly treatment regimens significantly increase the risk of OM. Treatment-related risk factors are directly related to the impact of radiotherapy and chemotherapy regimens on the oral mucosa. The repetitive effects of daily radiation treatments are responsible for the inflammation and ulceration of the oral mucosa. The dose and fractionation schedule of radiation determines the degree of OM, particularly in patients receiving radiation to the head and neck and patients receiving total body irradiation in preparation for bone marrow transplantation. Standard doses of common chemotherapy agents produce OM; these include the antimetabolites (e.g. 5-FU, methotrexate, etoposide), bleomycin, busulfan, cyclophosphamide, doxorubicin, vinblastine, vincristine, vinorelbine, and the taxanes. Higher doses of these agents may more than double the incidence of OM. Also, if

previous cancer treatment resulted in the development of OM, the likelihood of OM during subsequent cycles is greatly increased. Few cancers today are treated with single-modality therapies. Most are approached with a combination of chemotherapy and radiotherapy, often given concurrently. This combination significantly increases the risk and severity of OM.²⁰

Patient Assessment

OM requires the ongoing assessment and monitoring of the oral cavity. It should be systematically assessed pre-treatment to establish a baseline for all future comparisons, routinely during treatment, and post-treatment. The goal of these examinations is to improve or maintain a patient’s functional status.²¹ However, while the need for regular oral assessment is recognized, there is no consensus among the many existing clinical guidelines and oral care standards as to which rating/grading scales should be used. Ideally, a scale for OM should be objective, reliable, and valid for all clinical and research situations.²² To date, there are no universal standards of oral care and no assessment tools that fit all clinical settings.

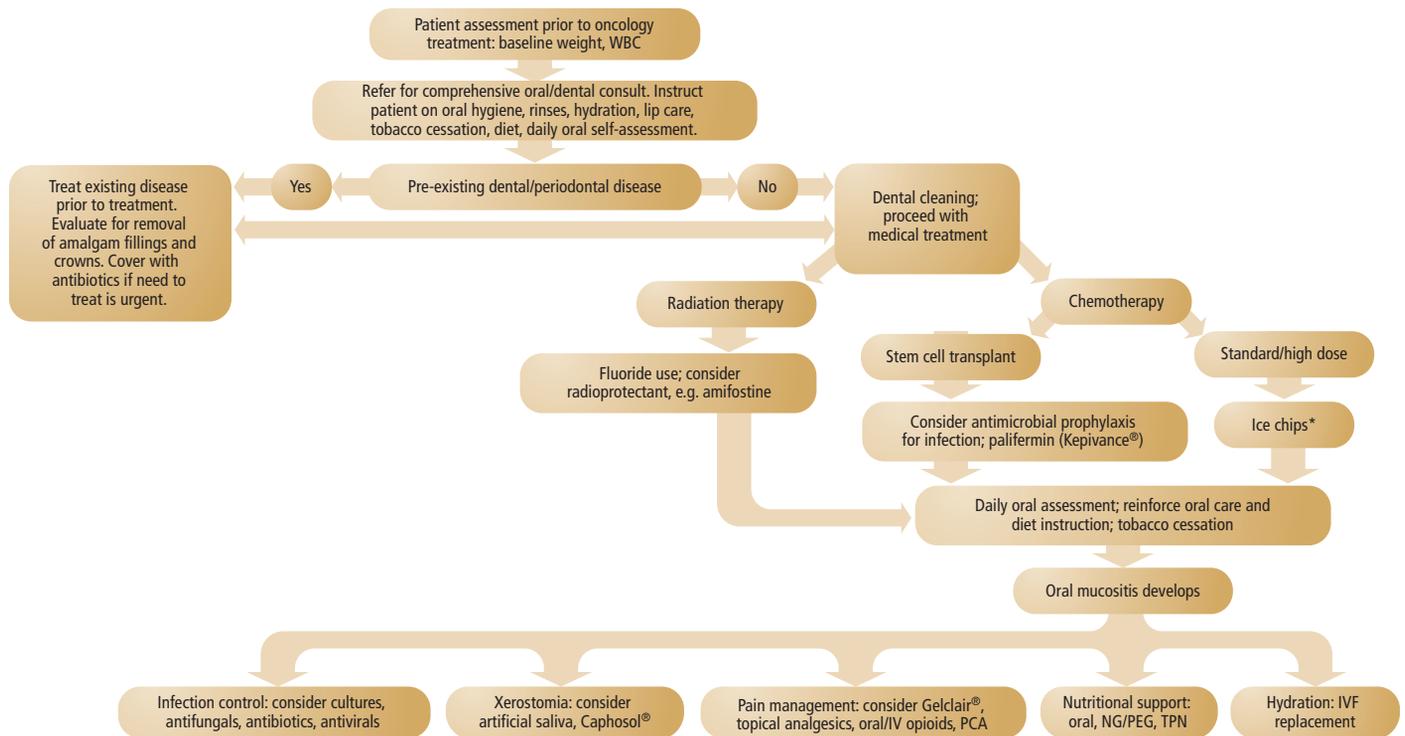
Preventive Strategies

OM can seldom be prevented. Therefore, the aim of treatment is to reduce its severity. Palifermin and amifostine are two products currently being used to reduce the extent and severity of OM. Palifermin is a recombinant KGF that stimulates the replication and maturation of epithelial cells. Palifermin has multiple mechanisms of action, including downregulation of pro-inflammatory cytokines, inhibition of epithelial cell DNA damage and apoptosis, and stimulation of epithelial cell growth, differentiation, and migration.²³ Palifermin has been approved in the US for use in patients with hematological malignancies who are undergoing total body irradiation and high-dose chemotherapy in preparation for peripheral blood stem cell transplant, in order to decrease the incidence and duration of severe OM. Phase III trials conducted by Spielberger et al.¹³ found that palifermin administered three days before transplant and three days after transplant showed a reduction in the incidence of grade 3 and 4 OM (63% with palifermin versus 98% with placebo). Spielberger found the duration of grade 3 and 4 OM was reduced from nine to six days with the use of palifermin. Amifostine is a radioprotectant that is currently approved for the prevention of radiation-induced xerostomia. In addition, the *United States Pharmacopoeia* recognizes an accepted off-label use of amifostine to reduce the incidence of mucositis in patients receiving chemotherapy or radiation alone, or in chemoradiotherapy.²⁴ This agent is believed to act as a free radical scavenger to protect healthy cells against the effects of radiotherapy or chemotherapy. The impact of amifostine on OM is probably due to an indirect effect related to the enhancement of saliva secretion, which has been demonstrated to reduce the intensity of mucositis.²⁵

Treatment Strategies

There are a number of targeted therapies in current use that aim to reduce the severity of OM and manage the associated pain. The most common interventions were identified in the ONS Mucositis Survey (see *Table 1*). More than three-quarters of respondents identified ‘magic mouthwash’ as their front-line approach for relief of OM pain. The formulation of ‘magic mouthwash’ varies among institutions, but typically consists of a mixture of lidocaine, diphenhydramine, and magnesium or aluminum hydroxide. Nystatin may be added to some of these formulations. Topical agents, such as ‘magic mouthwash,’ are often indicated in the management of mild to moderate OM pain, but remain predominantly palliative in nature. Pain reduction is minimal and of short duration. Patient compliance is

Figure 1: Treatment Algorithm for Patients at Risk for Oral Mucositis



Developed by the Oral Mucositis Working Group (see page 90).

* Ice chips x 30 minutes with bolus short-acting chemotherapy.

unpredictable, as the main drawback of these multimixture formulas is alterations in taste and the potential for further trauma to the oral tissue as a result of the numbness produced by the local anesthetic. There have been very few controlled clinical trials to determine the effectiveness of 'magic mouthwash' and compounded mouthwashes are not recommended in the MASCC guidelines (see *Table 3*). Sucralfate is a therapeutic agent that has been used in patients with peptic ulcer disease. Sucralfate is a basic aluminum salt of sucrose sulfate and is sometimes used as an oral suspension to treat OM. It produces a paste-like protective coating over the ulcerated mucosa. Sucralfate was believed to increase the local production of prostaglandin E2, leading to increased blood flow and production of mucus.²⁶ Prostaglandin E2 has been reported to have cytoprotective effects on a variety of tissues and can be a mucosal protectant in patients receiving high-dose chemotherapy. However, the effectiveness of sucralfate in treating OM is questionable and its use is not recommended by MASCC.

Gelclair® (EKR Therapeutics, Inc., Cedar Knolls, NJ) is the first concentrated oral gel indicated for the management of OM pain. Gelclair helps to soothe oral lesions of various etiologies—including OM caused by chemotherapy or radiation therapy—by adhering to the mucosa of the mouth and forming a protective barrier. The main ingredients of Gelclair include polyvinylpyrrolidone, hyaluronic acid, and glycyrrhetic acid. Polyvinylpyrrolidone is a hydrophilic polymer that acts as a muco-adherent and film-forming agent that enhances tissue hydration and accelerates wound healing in human wounds. Hyaluronic acid (or its sodium salt) is a viscous fluid that is naturally occurring in the body and promotes healing by hydrating mucous membranes, and acts as a protective film-forming, coating substance. Glycyrrhetic acid is a licorice extract that mediates healing through its anti-inflammatory properties. Gelclair contains no alcohol and no local anesthetic, so there is no drying of the mouth, no numbing, and no loss of taste. There have been few reported side effects

and no interactions with other medications. Gelclair has been shown to reduce the pain of OM for five to seven hours, both acutely and after long-term use.¹⁸ It is recommended that Gelclair be used three to four times per day. It has also been shown to be effective in alleviating pain following the ablation of soft tissue oral lesions after surgical laser treatment.²⁷ Gelclair may not eliminate the need for opiates, but may help delay the need to use them and decrease the amount required to control the pain of OM.

Caphosol® (Cytogen Corp., Princeton, NJ) is an electrolyte rinse comprising a phosphate solution and a calcium solution that must be mixed together in a glass. It is indicated as an adjunct to standard oral care in treating OM caused by radiation or high-dose chemotherapy. Relief of dryness of the oral mucosa in these conditions is associated with an amelioration of pain. It is also indicated for dryness of the mouth or throat, regardless of the cause or whether the conditions are temporary or permanent. Caphosol lubricates the mucosa and helps maintain the integrity of the oral cavity through its mineralizing potential. The distinguishing feature of Caphosol is its high concentrations of calcium and phosphate ions, which are hypothesized to exert their beneficial effects by diffusing into intracellular spaces in the epithelium and permeating the mucosal lesion in mucositis.²⁸ A prospective, randomized, double-blind, placebo-controlled trial demonstrated Caphosol to be a significant adjunct in the management of mucositis associated with high-dose chemotherapy and radiation therapy. The study evaluated the severity of OM and the requirements for opioid medication in 95 patients undergoing hematopoietic stem cell transplantation. Results indicated that Caphosol significantly reduced the duration and severity of OM, as well as the need for opioid medications.²⁹ In severe OM, Caphosol may be required as often as 10 times per day for the duration of cancer treatment.

Opiates have been the cornerstone of pain management for moderate to

severe OM. They are often started at the onset of pain and titrated throughout the treatment phase or until the OM has resolved. Opiates are the best-studied approach for the management of severe OM pain. The WHO recommends morphine as the opioid of choice for the management of severe pain.³⁰ Elting and colleagues³¹ found that although 37% of patients identified significant pain with OM, only 8% of patients received opiates. The effective use of opiates requires balancing the desired effects of pain relief with undesired side effects, such as constipation, nausea and vomiting, and sedation. Despite the use of opiates, many patients still need hospitalization for dehydration, weight loss, and placement of feeding tubes. Clearly, there are many treatments available to help alleviate the pain of OM, and most have a degree of efficacy in particular patients. The question for the healthcare practitioner is which treatment should be used for which patient at which stage of OM. Based on their varied clinical experiences, the OM Working Group has developed a treatment algorithm for patients at risk for OM. This algorithm incorporates the latest recommendations of the MASCC guidelines and is a practical guide for the day-to-day management of OM. It is also easily adaptable to a variety of practice settings (see *Figure 1*).

Summary

OM presents a frustrating challenge for healthcare providers and a painful obstacle for patients. Among all the treatment side effects and complications that cancer patients face, OM ranks as one of the most troublesome. There is now a better understanding of the underlying pathophysiology of OM and the complexity of mucosal injury, which provides some insight into whether or not standard treatments will ameliorate symptoms, prevent tissue damage, or, conversely, interfere with the healing process. Multiple treatments with different modes of action may be required to treat OM effectively. Frequently, healthcare providers do not have any treatment guidelines to assist them in managing OM. Data collected at the most recent ONS Congress (April 2007) indicated that the large majority of cancer nurses do not apply a systematic approach to

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managing OM interventions in their individual clinical settings. Many also lack a valid and reliable assessment tool for OM. Finally, more research is needed in all facets of OM—cellular and molecular biology, prophylaxis and treatment, and predicting which patients are at risk. It is astounding that more than two-thirds of oncology nurses rate OM interventions as only minimally effective and, in fact, the most commonly used preparation is not recommended by the MASCC guidelines. Evidence-based treatments will help to improve patient outcomes and, ultimately, quality of life. ■

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Special precautions for use: Avoid eating or drinking for at least 1 hour after use. Do not use any packet that is not intact (torn, split, or otherwise damaged in any way). If no improvement is noticed after 7 days, consult a physician.

Keep out of the reach of children.

Warning: Federal law restricts GELCLAIR® to sale by or on the order of a physician or properly licensed practitioner.

Interaction with other medicinal products and other forms of interaction: There are no known interactions with medicinal or other products.

Directions for use: Pour the entire contents of the single-use GELCLAIR® packet into a glass and add 1 tablespoon of water. If this dilution of GELCLAIR® is too thick, it may be diluted with an additional 1-2 tablespoons of water to achieve the desired thickness. Stir mixture well and use immediately. Rinse around the mouth for at least 1 minute or as long as possible to coat tongue, palate, throat, inside of cheeks, and all oral tissue thoroughly. Gargle and spit out. Use 3 times a day or as needed. Do not eat or drink for at least 1 hour following treatment. If water is not available, GELCLAIR® may be used undiluted. If GELCLAIR® is swallowed accidentally, no adverse effects are anticipated.

Side effects: At the time of producing this leaflet, no adverse effects have been reported in clinical trials with the use of GELCLAIR®. Postmarketing reports have included infrequent complaints of burning sensation in the mouth.

Overdose: At the time of producing this information, no cases of overdose have been reported.

Storage: Store at room temperature, out of direct sunlight. The gel may become a little darker and thicker over time, but this does not affect its efficacy or safety. Do not use after the expiration date shown on the box and packet.

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