MMI Script Hub and Medical Supplies LLC
Medicare Part B Supplier
Practice/Supplier's Address: 1768 Storrs Road Storrs Connecticut 06268
Tel: 860.477.0961 Fax: 860.477.0962 NPI 1063884146 PTAN D100466287

Submitted by: MMI Script Hub and Medical Supplies
Name: Ricky McCullough MD, ScM, FAcadTM
Company/Organization: Mueller Medical International LLC
Address: 1768 Storrs Road, Storrs-Mansfield, CT 06268
Phone: 860-477-0961
Email: mmi.sh.medsupL@muellermedical.com
Date of request: June 18, 2020
NCCN Guidelines Panel: ADULT CANCER PAIN
Algorithm Page: PAIN-D

On behalf of Mueller Medical International, I respectfully request the NCCN ADULT CANCER PAIN Panel to review the enclosed data for inclusion of the Polymerized Cross-linked Sucralfate (PCLS, ProThelial®) for the management of oral, pharyngeal and esophageal mucositis.

Specific Changes: Recommend the use of polymerized cross-linked sucralfate for the management of cancer treatment related mucositis occurring in the oral cavity, pharynx, esophagus and gastrointestinal tract.
FDA Clearance: Polymerized cross-linked sucralfate (PCLS) is FDA-cleared in August 2013 for the management of mucositis and stomatitis under FDA application 510k-123904 [1].
Rationale: Evidence-based statistics from a Phase IV study of PCLS prescribed by 26 radiation oncologists and 13 medical oncologists treating oral, pharyngeal, esophageal and GI mucositis caused by 15 distinct anti-neoplastic (chemo-, immuno-, radiation) regimens for 11 tumor types in 66 patients revealed a 97% reduction in the duration of mucositis, its tissue damage and of patient reported pain from the usual 84 days **[2]** to 2.5 days, with mucosal reversal being sustained by PCLS throughout continued chemoradiation therapy.
Key Literature Citation: The Phase IV data was reported in Journal of Oncology Pharmacy Practice **[3]**, Journal of the Academy of Oncology Nurse Navigators **[4]**, the European Oncology Pharmacy Journal **[5]**, the Korean Journal of Clinical Oncology **[6]** and Future Oncology **[7]** . The publication in Journal of Supportive Care in Cancer **[8]** was presented in 2019 Annual MASCC meeting and was entitled: High Potency Polymerized Cross-linked Sucralfate (HPPCLS, ProThelial) for NCCN Category 2A evaluation to prevent and rapidly eliminate chemoradiation toxic mucositis.

Quality of Evidence:
Evidence-based criteria established by G.R.A.D.E. (Grading of Recommendations, Assessment, Development and Evaluation) classify the quality of evidence from Phase IV PCLS as GRADE A which means high **[9]**. This is largely due to the quantitative size of treatment effect observed in consistently and repeatedly lowering anticipated 84 day duration of mucositis to 2.5 days, which was greater than 5 standard deviations from expected. This 97% reduction in mucositis duration occurring regardless of clinical scenario, coupled with the known dose-gradient effect of PCLS **[10]**, qualifies PCLS as a GRADE Category 1B recommendable intervention **[11, 12].**

Background on Mucositis Pain as an Emergency Condition
Mucositis pain has been a longstanding problem dreaded by most oncologists [13, 14]. In 2002, AHRQ Publication No. 02-E032 (Agency for Health and Research Quality, CMS) identified tissue damage-associated pain of chemoradiation mucositis (CRM) as a grave problem **[15]**, In 2010, AHRQ Publication No. 10-EHC014-EF **[16]** and in 2014, AHRQ Publication No.15-EHC001-EF **[17]**, confirmed that CRM was "painful"…"disfiguring"…"debilitating and dose-limiting". The latter consequence of CRM, that of being dose-limiting, impacts 5 year survival. While infections associated with oral and GI mucositis account for 5% of all HSCT deaths **[18],** the remaining 45,000 annual CRM associated deaths **[7]** stem from patient/physician decision to limit chemoradiation dose due to the pain of CRM. Limiting radiation dose in head neck cancer patients for just 3 days in the third week of a 42-day regimen can lower 5 year survival from 65% to 18% **[6,7, 19].** Thus according to

Medicare rules **[20]** (as well as those of Public Health Service Act, Patient Protection Affordability Act and Social Security Act), the symptom complex of CRM classifies the acute pain and dysfunction syndrome as an emergency medical condition **[20]** requiring an antidote. Distinct from other anti-mucositis agents (Kepivance, MuGard, Episil, Caphasol, Gelclair, local anesthetic formulations), the PCLS Phase IV data and its current continued use, have shown PCLS rapidly alters the course of CRM toxicity, reversing ulcerated painful mucosa to normal as would be expected for an antidote. When insurers disagreed that PCLS was an antidote, the Department of Health and Human Services ruled in December 2019 that ProThelial (PCLS) administered to manage CRM is an emergency therapy and in accordance to Federal Rules insurers must cover PCLS without prior authorization **[21]**. Besides being an antidote to CRM, PCLS reduces overall costs of CRM care by 40-60% **[22]**, an outcome reflected in the NCCN Evidence Block evaluation of PCLS.

NCCN Evidence Block Evaluation of PCLS

Oncologists are most familiar with NCCN Evidence Block (EB) approach in assessing an intervention **[23]**. The 5x5 matrix based on a 1-5 scoring of treatment's efficacy, safety, quality of evidence, consistency of evidence and affordability provides a visual assessment of value useful for patients and payers **[24]**. NCCN EB evaluation of PCLS has been published **[8]**. Regarding EB-efficacy, PCLS showed a 97% reduction in mucositis duration, a high Cohen-D value of 4.1, (on a scale of 0.3 to 0.8), a Glasziou rate ratio of 62.3 exceeding required rate ratio threshold of 10, all of which yields an EB efficacy rating of 5/5. Regarding EB-safety, negligible adverse events were observed with PCLS or sucralfate, yielding an EB rating of 5/5. Regarding EB-evidence quality, requisite G.R.A.D.E criteria rated PCLS evidence at a Level 1 Category B yielding an EB 4/5 rating. Regarding EB-evidence consistency, the ROBINS-I analysis of PCLS trial revealed low risk of bias in all 7 ROBINS-I domains yielding a low EB rating of 3/5. Regarding EB-affordability, PCLS reduced mucositis costs of care by 40 to 60% yielding an EB rating of 5/5. PCLS's overall NCCN Evidence Block rating is 4.4 out of total of 5. Current NCCN mucositis pain interventions in Algorithm page PAIN-D are unlikely to have an equivalent EB rating.

Current NCCN Mucositis Pain Treatments – Gabapentin/Local Anesthetic/Oral Care

Algorithm page PAIN-D of Version 1.2020 NCCN Guidelines for Adult Cancer Pain recommends interventions proven to only fractionally alter the course of mucositis pain **[5, 25]**. The size for the treatment effect for current NCCN interventions are at least 10 fold smaller than that of PCLS **[see Figure 1, Ref 3 or Figure 2, Ref 4]**. Pharyngeal, esophageal and GI mucositis cannot be managed by "local anesthetic formulations/ oral care protocols" while PCLS has demonstrated reversal of mucositis pain from oral cavity to the GI tract without local anesthetics or oral care.

MASCC New Position on Sucralfate for Mucositis

After 15 years of "recommending against" the use of sucralfate for mucositis pain **[26]**, MASCC reversed its position to that of neutral **[27]** in 2020**,** citing as their rationale the "new [clinical] results" associated with PCLS as reported in the Journal of Oncology Pharmacy Practice **[3]**.

Conclusions and Request for Specific Guideline Changes

Unlike other therapies that do not alter the course of CRM (reverse its toxicity and pain), PCLS does and in so doing address all "5 A's" of pain management. Based on this –addressing all "5 A's" of pain management- and on the aforementioned rationale, quality of evidence review, background on mucositis pain as an emergency condition compelling coverage by insurers and the NCCN Evidence Block assessments, we request that the Adult Cancer Pain Panel amend current guidelines to "**Recommend the use of polymerized cross-linked sucralfate for the management of cancer treatment related mucositis occurring in the oral cavity, pharynx, esophagus and gastrointestinal tract**."

Respectfully

Ricky McCullough MD, ScM, FAcadTM, Medical Director,
On behalf of Mueller Medical International
Attachments to Letter/Email: 1. Reference List / 2. Selected Publications

CITED REFERENCES: Adult Cancer Pain Panel for Polymerized Cross-linked Sucralfate

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