ONAMER® M

PRESERVATIVE and ANTIMICROBIAL

ONAMER® M

Stepan® Lipid Nutrition

The Natural Way to Better Health

Stepan Lipid Nutrition is a division of Stepan Company which manufactures lipid and polymer based ingredients.

SUMMARY

Our quaternary ammonium polymer ONAMER M is a biocide agent which can be used as a preservative, unique in its high safety profile. ONAMER M is selected especially when contact to sensitive tissue is required in the drug formulation (as with skin, eyes and other mucous membranes). ONAMER M is manufactured under regulatory quality compliance to FDA and ICH Q7A, cGMP guidelines, which includes a registered DMF (Drug Master File) and technical dossier.

ONAMER M belongs to the class of antimicrobial quaternary ammonium compounds (QACs). At least two specific characteristics are found in ONAMER M compared to most other QACs: First is the absence of foaming even in high concentrations, and second is its remarkably low toxicity (up to 20 times less toxic than other QACs). In addition, ONAMER M is fairly stable under high heat conditions, which allows autoclaving of fluids preserved by ONAMER M.

SAFETY DATA ON ONAMER M

ONAMER M is a very safe preservative, which shows very low acute toxicity in rats. An LD50 was observed at 4.47 ml/kg of a preparation containing 40% active material. This low toxicity is probably related to low uptake from the gastrointestinal tract which is related to its relatively high molecular weight and to its positive charge.

The potential mutagenicity of ONAMER M was tested in an *in vitro* assay (Mouse lymphoma TK gene mutation test) and in an *in vivo* assay (Drosophila melanogaster sex-linked recessive lethal mutation test). ONAMER M was free of mutagenic activity in both tests.

The potential carcinogenicity of ONAMER M was evaluated in the 3T3 cell transformation tests. This showed a complete lack of carcinogenic potential of ONAMER M.

ONAMER M concentrations of up to at least 40,000 ppm (or 4%) are non-eye irritating, although concentrations as low as 10 ppm show bactericidal activity in lens fluids. This provides a very high safety margin of at least 4,000 times. ONAMER M is also non-irritating to the skin (in up to 40% active material), and has no activity as a dermal sensitizer in humans.

Our overall safety data shows that ONAMER M has a very wide safety window which ensures its safe use in topical applications and where contact of drugs with sensitive tissue is required.

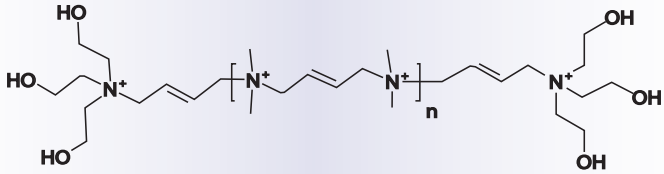

Figure 1.
The chemical structure of ONAMER M. The chemical name of ONAMER M is α-4-[1-tris(2-hydroxyethyl) ammonium chloride-2-butenyl] poly [1-dimethyl ammonium chloride-2 butenyl]-ω-tris(2-hydroxyethyl) ammonium chloride.

Table 1 – SAFETY DATA ON ONAMER M

TEST	RESULTS
Acute oral toxicity (rat, n=10)	LD50 = 4.47 ml/kg (slightly toxic)
Primary eye irritation (rabbit, n=3)	Non-irritating at 4% active ingredient
Eye lens incubation safety study (rabbit, n=3)	Non-irritating at 3% active ingredient
Primary skin irritation study (rabbit, n=6)	Non-irritant at 40% active ingredient
Human *in vivo* skin sensitization test (n=55)	Non-sensitizing (ONAMER M batch: OM-180-372)
Mouse lymphoma mutagenicity test (*in vitro*)	Not mutagenic
Sex-linked recessive lethal test (Drosophila)	Not mutagenic
***In vitro* transformation test in 3T3 cells**	Not transforming
Acute aquatic toxicity	LC50 = 0.35 mg/l (highly toxic)

ANTIMICROBIAL EFFECTS OF ONAMER M

Typical antimicrobial therapies including systemic antibiotics such as gentamycin, methicillin, and cephalosporins have been used for years to prevent infections and reduce colonization. However, the widespread use of systemic antibiotics has lead to the evolution of multi-drug resistant bacteria such as VRE (vancomycin resistant Enterococci) and MRSA (multi-resistant Staphylococcus aureus) that are resistant to antibiotics.

Alternatively, antiseptics including alcohols, biguanides (including chlorohexidine), bisphenols, heavy metals (such as silver compounds), peroxygens, and quaternary ammonium compounds have also been used to prevent bacterial growth. However the undesirable aspect of these antiseptic treatments is that they can be toxic and cause further damage, especially when used at their effective doses.

ONAMER M may provide a solution to several safety challenges of typical antimicrobials and antiseptics.

The data in Table 2 show that ONAMER M displays efficacy and antimicrobial activity comparable and in some cases shows improvement over Benzalkonium chloride and chlorohexidine gluconate across a wide range of microbes. ONAMER M is effective at inhibiting common gram positive and gram negative bacteria as well as certain fungal species. The study shows that ONAMER M is also effective at inhibiting growth of multi-drug or methicillin resistant bacteria (MRSA).

Table 2 – MINIMUM INHIBITORY CONCENTRATION (MIC) STUDY

BACTERIA		MIC (ppm)		
		ONAMER M	BTC 50 NF	CHG
Gram Positive Bacteria	Bacillus cereus	75	nd	nd
	VRE	>100	nd	nd
	Staphylococcus epidermidis	≤10	≤10	≤10
	Staphylococcus aureus	≤10	≤10	≤10
	MRSA	≤10	≤10	≤10
Gram Negative Bacteria	Pseudomonas aeruginosa	≤10	50	25
	Escherichia coli	≤10	≤10	≤10
	Yersinia enterocolitica	≤10	≤10	≤10
Fungi-Yeast	Candida albicans	>100	nd	nd

Table 2.
ONAMER M, Chlorohexidine gluconate (CHG) and Benzalkonium chloride (BTC) were compared with respect to the minimum inhibitory concentration (MIC) for various gram positive and negative bacteria as well as for Candida albicans.

ONAMER® M

In Table 3, data are presented of an *in vitro* time kill experiment. This data shows the effectiveness of ONAMER M against selected clinically and environmentally significant microbes (including yeast) at various concentration and contact times. At 100 ppm of ONAMER M and at a contact time of 60 seconds or less, a significant kill was reported both for gram positive and gram negative bacteria. At a contact time of 5 minutes, this dose of ONAMER M also demonstrated effectiveness against MRSA. At a contact time of 24 hours at both 100 and 200 ppm of ONAMER M, all tested microorganisms were killed.

Table 3 – *IN VITRO* TIME KILL STUDY

TEST SUBSTANCE	BACTERIA	KILL RATE VS. CONTACT TIME			
		30 SEC.	1 MIN.	5 MIN.	24 HRS.
ONAMER M 100 ppm active	Bacillus cereus	Y	Y	Y	Y
	VRE	N	N	N	Y
	Staphylococcus aureus	N	N	N	Y
	MRSA	N	N	Y	Y
	Pseudomonas aeruginosa	Y	Y	Y	Y
	Candida albicans	Y	Y	Y	Y
ONAMER M 200 ppm active	Bacillus cereus	Y	Y	Y	Y
	VRE	N	N	N	Y
	Staphylococcus aureus	N	N	N	Y
	MRSA	N	Y	Y	Y
	Pseudomonas aeruginosa	Y	Y	Y	Y
	Candida albicans	Y	Y	Y	Y

Table 3.
ONAMER M was tested in a time kill experiment. This experiment demonstrates the effectiveness of ONAMER M against selected clinically and environmentally significant microbes (including yeast) at various concentration and contact times. "Y": Less than 10% survival, "N": More than 10% survival.

ABOUT ONAMER M

INCI Name: Polyquaternium-1

INN Name: Polidronium Chloride

CAS Number: 75345-27-6

TYPICAL PROPERTIES	
APPEARANCE	Clear, amber to dark brown viscous liquid
ODOR	Mild Characteristic
SOLIDS	40%
CHLORIDE CONTENT	10%
ASSAY	33%
FREE AMINE	2%
pH	7.3
SOLUBILITY IN WATER	Complete

SUGGESTIONS FOR MARKETS AND APPLICATIONS*

- Preservative/Antimicrobial options include:
  - ✓ Products targeting mucosal membranes or other sensitive tissue
  - ✓ Liquid Pharmaceutical Preparations & Solutions such as:
    - Ear (Otic)
    - Nasal
    - Inhalants
    - Sprays
    - Suspensions
    - Gels

**Certain applications for ONAMER M are restricted due to trade secrets. Check with a Stepan representative for details.*

MISCELLANEOUS INFORMATION

- Drug Master File (DMF) is available
- Samples available
- Safety studies available
- Analysis data available

Usage of antimicrobial compounds in the presence of high levels of microbial contamination can have a significant effect on the product's biocidal activity. However, ONAMER M appears to maintain an excellent level of antimicrobial efficacy despite repeated challenges (data provided on request).

Wound Care Model

In order to evaluate the effects of ONAMER M in wound care, ONAMER M was applied to superficial wounds on pigs. The test animals had been inoculated on the previous day with Pseudomonas aeruginosa (PA) or MRSA. The antimicrobial activity of ONAMER M against MRSA in this model is shown in Figure 2. Mupirocin, a standard treatment for MRSA bacteria, was used as a positive control.

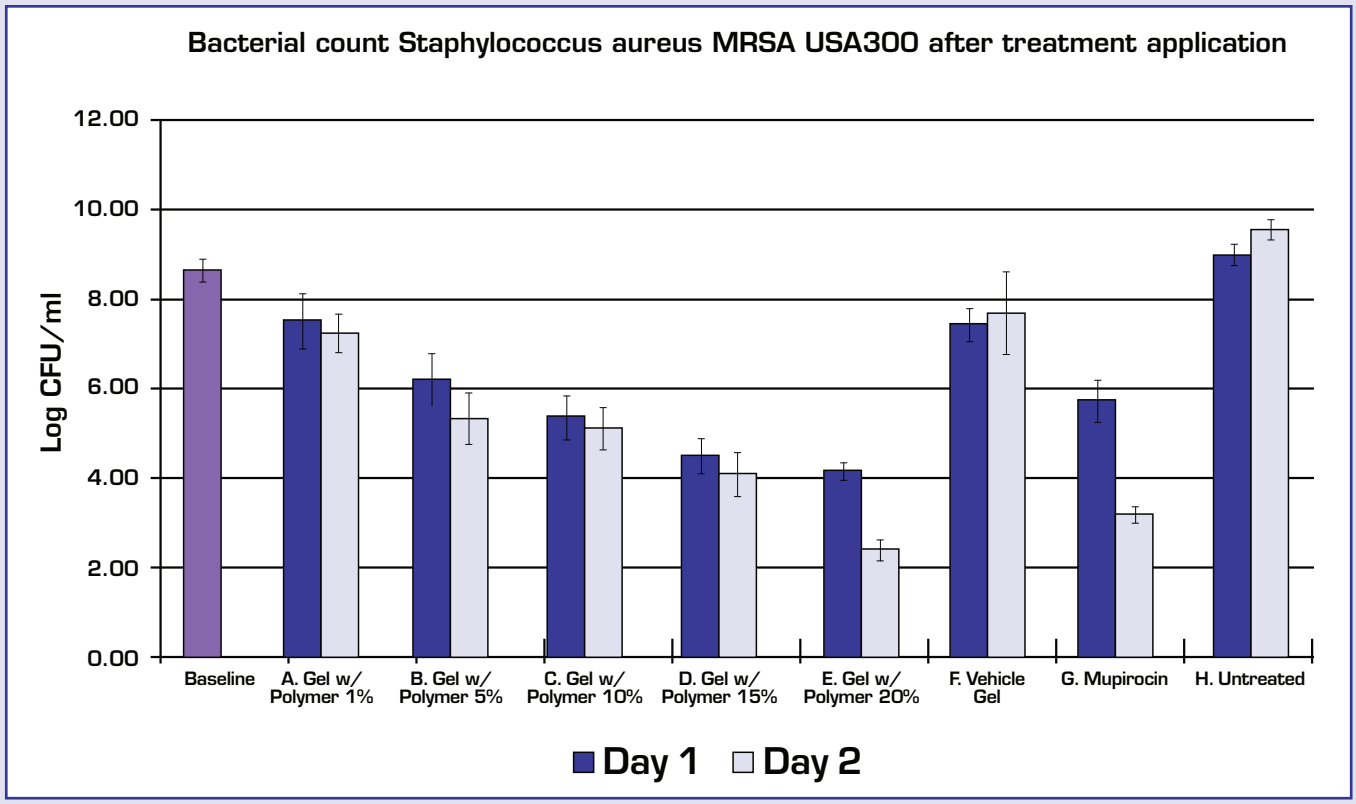

Figure 2.
After a superficial wound had been inoculated with MRSA bacteria for one day, ONAMER M (Polymer), formulated in a simple gel formulation, was dosed to the wounds. The log reduction in the number of bacteria, on day 1 and day 2 after treatment is shown in this figure. (Two logs reduction means 99% kill).

MECHANISM OF ACTION OF ONAMER M

The mechanism of antimicrobial action is believed to be very similar to the action of other quaternary ammonium compounds. This mechanism is based on the fact that the outermost cell surfaces of bacteria carries a negative charge associated with the bacterial cell wall (polysaccharides) that is stabilized by positively charged ions (Mg^{2+} and Ca^{2+}). ONAMER M is also positively charged and has a high binding affinity for bacteria. The ingredient integrates into the membrane and is thought to inhibit bacterial growth and cause membrane perturbations and cellular death.

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