

[0161] Frequency of dosage may also vary depending on the compound used and the particular disease treated. It will also be appreciated that the effective dosage of the compound used for treatment may increase or decrease over the course of a particular treatment. Changes in dosage may result and become apparent by standard diagnostic assays known in the art. In some instances chronic administration may be required. The compounds of the present invention may be administered before, during, after, or a combination thereof exposure to bacteria.

[0162] As provided herein, an “effective amount” is intended to mean that amount of a compound that is sufficient to reduce, prevent or inhibit BoNT/A LC metalloprotease activity as compared with a negative control. A “therapeutically effective amount” of a compound of the present invention, a prodrug, an active metabolite, or a salt thereof, is a quantity sufficient to, when administered to a subject, reduce, prevent or inhibit BoNT/A LC metalloprotease activity. Also, as used herein, a “therapeutically effective amount” of a compound of the present invention is an amount which prevents, inhibits, suppresses, or reduces a given clinical condition in a subject as compared to a control. As defined herein, a therapeutically effective amount of a compound of the present invention may be readily determined by one of ordinary skill by routine methods known in the art.

[0163] The pharmaceutical formulations of the invention comprise at least one compound of the present invention and may be prepared in a unit-dosage form appropriate for the desired mode of administration. The pharmaceutical formulations of the present invention may be administered for therapy by any suitable route including oral, rectal, nasal, topical (including buccal and sublingual), dermal, mucosal, vaginal and parenteral (including subcutaneous, intramuscular, intravenous and intradermal). It will be appreciated that the preferred route will vary with the condition and age of the recipient, the nature of the condition to be treated, and the chosen compound of the present invention.

[0164] The compound can be administered alone, but will generally be administered as pharmaceutical formulations suitable for administration. Pharmaceutical formulations known in the art contemplated herein. Pharmaceutical formulations of this invention comprise a therapeutically effective amount of at least one compound of the present invention, and an inert, pharmaceutically or cosmetically acceptable carrier or diluent. As used herein the language “pharmaceutically acceptable carrier” or a “cosmetically acceptable carrier” is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical or cosmetic administration. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the formulation is contemplated. Descriptions of suitable pharmaceutically acceptable carriers, formulations, and factors involved in their selection, are found in a variety of readily available sources, e.g., Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, which is incorporated herein by reference.

[0165] Supplementary active compounds can also be incorporated into the formulations. Supplementary active compounds include antibiotics, antiprotozoal agents, antifungal agents, and antiproliferative agents known in the art, analgesics and other compounds commonly used to treat diseases and disorders associated with bacterial infection and toxic

side effects of bacterial infection including intoxication by a toxin. Supplementary active compounds also include those known in the art which delay toxin induced muscle paralysis such as BoNT/A holotoxin induced muscle paralysis.

[0166] Antibiotics include penicillin, cloxacillin, dicloxacillin, methicillin, nafcillin, oxacillin, ampicillin, amoxicillin, bacampicillin, azlocillin, carbenicillin, mezlocillin, piperacillin, ticarcillin, azithromycin, clarithromycin, clindamycin, erythromycin, lincomycin, demeclocycline, doxycycline, minocycline, oxytetracycline, tetracycline, quinolone, cinoxacin, nalidixic acid, fluoroquinolone, ciprofloxacin, enoxacin, grepafloxacin, levofloxacin, lomefloxacin, norfloxacin, ofloxacin, sparfloxacin, trovafloxacin, bacitracin, colistin, polymyxin B, sulfonamide, trimethoprim-sulfamethoxazole, co-amoxycylav, cephalothin, cefuroxime, ceftriaxone, vancomycin, gentamicin, amikacin, metronidazole, chloramphenicol, nitrofurantoin, co-trimoxazole, rifampicin, isoniazid, pyrazinamide, kirromycin, thiostrepton, micrococin, fusidic acid, thiolactomycin, fosmidomycin, and the like.

[0167] Antiprotozoal agents include chloroquine, doxycycline, mefloquine, metronidazole, eplornithine, furazolidone, hydroxychloroquine, iodoquinol, pentamidine, mebendazole, piperazine, halofantrine, primaquine, pyrimethamine sulfadoxine, doxycycline, clindamycin, quinine sulfate, quinidine gluconate, quinine dihydrochloride, hydroxychloroquine sulfate, proguanil, quinine, clindamycin, atovaquone, azithromycin, suramin, melarsoprol, eflornithine, nifurtimox, amphotericin B, sodium stibogluconate, pentamidine isethionate, trimethoprim-sulfamethoxazole, pyrimethamine, sulfadiazine, and the like.

[0168] Antifungal agents include amphotericin B, fluconazole, itraconazole, ketoconazole, potassium iodide, flucytosine, and the like.

[0169] Antiproliferative agents such as altretamine, amifostine, anastrozole, arsenic trioxide, bexarotene, bleomycin, busulfan, capecitabine, carboplatin, carmustine, celecoxib, chlorambucil, cisplatin, cisplatin-epinephrine gel, cladribine, cytarabine liposomal, daunorubicin liposomal, daunorubicin daunomycin, dexrazoxane, docetaxel, doxorubicin, doxorubicin liposomal, epirubicin, estramustine, etoposide phosphate, etoposide VP-16, exemestane, fludarabine, fluorouracil 5-FU, fulvestrant, gemcitabine, gemtuzumab-ozogamicin, goserelin acetate, hydroxyurea, idarubicin, ifosfamide, imatinib mesylate, irinotecan, letrozole, leucovorin, levamisole, liposomal daunorubicin, melphalan L-PAM, mesna, methotrexate, methoxsalen, mitomycin C, mitoxantrone, paclitaxel, pamidronate, pegademase, pentostatin, porfimer sodium, streptozocin, talc, tamoxifen, temozolamide, teniposide VM-26, topotecan, toremifene, tretinoin, ATRA, valrubicin, vinorelbine, zoledronate, steroids, and the like.

[0170] Supplementary active compounds also include other compounds known in the art which inhibit botulinum neurotoxin serotype A light chain metalloprotease activity, anthrax lethal factor protease activity, or a combination thereof such as NSC 240898, NSC 266474, NSC 266476, NSC 290107, NSC 290108, NSC 290109, NSC 294200, NSC 294201, NSC 294203, NSC 294204, NSC 294206, NSC 300511, NSC 308571, NSC 308572, NSC 308574, NSC 317880, NSC 317881, NSC 317884, NSC 317885, 317886, NSC 317887, NSC 341907, NSC 341909, and NSC 341911.

[0171] Toxicity and therapeutic efficacy of such compounds can be determined by standard pharmaceutical pro-