Loratadine for Improvement of Bone Pain in Patients with Chronic Granulocyte-Colony Stimulating Factor (G-CSF) Use

NCT03883386

Document Date: 02/04/2019

Loratadine for Improvement of Bone Pain in Patients with Chronic Granulocyte-Colony Stimulating Factor (G-CSF) Use

Principal Investigator
Kelly Walkovich, MD
Department of Pediatrics
Division of Hematology/Oncology
University of Michigan

Co-investigators
David Frame, PharmD
College of Pharmacy
University of Michigan

Thomas Michniacki, MD
Department of Pediatrics
Division of Hematology/Oncology
University of Michigan

Lauren Merz, BA
Medical School
University of Michigan

Revision Date: 02/04/19

Table of Contents

Study Schema

1. Background

Uses and mechanism of granulocyte-colony stimulating factor (G-CSF)
Granulocyte-colony stimulating factor G-CSF is a glycoprotein that stimulates the bone marrow to produce granulocytes resulting in an increased number of circulating neutrophils. G-CSF is most often used to increase neutrophil counts in patients receiving myelosuppressive chemotherapies to reduce the duration of febrile neutropenia by enhancing neutrophil recovery, or to reduce the infectious and wound healing complications of neutropenia in patients with severe congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia. Common forms of G-CSF include filgrastim, pegfilgrastim, and lenograstim.

Incidence of bone pain in patients using G-CSF
The incidence of bone pain secondary to G-CSF in patients with severe congenital neutropenia, cyclic neutropenia, or idiopathic neutropenia is not well reported. Additionally, reported incidences of bone pain in healthy donor and cancer patients vary with different formulations of G-CSF and for different indications of use. For example, the package insert for general use of filgrastim reports bone pain occurrence in 24% of patients and 31% of patients using pegfilgrastim. However, other studies of filgrastim and pegfilgrastim in cancer patients reports bone pain in 25-38%[1-3]. Studies of healthy donors using G-CSF report bone pain in 52-84% of patients[1, 4, 5].

Mechanism of Bone pain from G-CSF
G-CSF is often used chronically in patients with diseases such as severe congenital neutropenia, cyclic neutropenia and idiopathic neutropenia. Bone pain is a common side effect of G-CSF. The exact mechanism underlying this bone pain is unknown. Some theories include that the pain is caused by increases in hematopoietic progenitor cells that increase bone marrow pressure, edema in bone marrow from histamine release, and increased levels of bradykinin[1, 6-8]. Additionally, receptors for G-CSF have been found on nerve fibers that may be involved in pain modulation[9, 10].

Loratadine for bone pain during chemotherapy
Naproxen or Loratadine and Neulasta (NOLAN) clinical trial[11]. This 2016 study of 600 patients assessed the difference in bone pain in breast cancer patients receiving chemotherapy and pegfilgrastim and either no prophylactic intervention, prophylactic naproxen, or prophylactic loratadine. This study found no significantly significant difference in bone pain between no prophylaxis, naproxen, and loratadine. However, loratadine was associated with fewer treatment-related adverse events and discontinuations compared to naproxen.

Evaluation of Loratadine for Prevention of Pegfilgrastim-Induced Pain[12]. This 2013 study determined the incidence of pegfilgrastim-induced back and leg pain in cancer patients and evaluated if loratadine is an effective prophylactic strategy to prevent bone pain. This study found that prophylactic loratadine does not decrease the incidence of bone pain in this patient population.

Evaluation of Loratadine for G-CSF Induced Bone Pain in Patients With Hematologic Malignancies[13]. This is a clinical trial that has not yet disseminated results assessing the effectiveness of loratadine in decreasing the incidence and severity of bone pain following G-CSF administration in patient with hematologic malignancies.

Loratadine for bone pain for patients using G-CSF for non-malignant indications
There is very little literature on loratadine for treatment of bone pain in patients using G-CSF for non-malignant indications such as idiopathic neutropenia, cyclic neutropenia or severe congenital neutropenia. Currently, all the robust literature and clinical trials address the use of loratadine in patients using G-CSF with bone pain during myelosuppressive chemotherapy for various cancers or for blood cancers. Anecdotally, loratadine has been used for bone pain in patients using G-CSF for diseases like severe congenital neutropenia[14, 15], but there is no literature specifically describing the efficacy of loratadine for bone pain in chronic G-CSF use in patients with non-malignant chronic diseases.

2. Rationale and Specific Aims

Patients who have non-malignant forms of neutropenia such as severe congenital neutropenia, cyclic neutropenia and idiopathic neutropenia often require chronic G-CSF use to abrogate the risk of infectious complications and promote wound healing. G-CSF is known to frequently cause bone pain[1, 11, 12, 14]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are a common first line treatment for bone pain[2, 11, 15]. However, NSAIDs can have side effects such as stomach ulcers or kidney toxicity. Additionally, NSAIDs may be ineffective for G-CSF related bone pain. Chronic bone pain can negatively impact quality of life, and impact long-term adherence to G-CSF. Although there is data on loratadine for bone pain with G-CSF use in patients with cancer, there is not currently robust data on loratadine for bone pain in chronic G-CSF use for non-malignant indications. Therefore, it is critical to carefully determine the efficacy of loratadine vs placebo for bone pain and for the quality of life in patients using G-CSF for non-malignant indications.

Specific Aim I: *To determine the incidence and severity of bone pain in patients using G-CSF for non-malignant indications*.

We hypothesize that 50% of our patients chronically using G-CSF for non-malignant indications (>3 months, at least 4x each month) will have bone pain of at least a mean of 3/10 as assessed by the Brief Pain Inventory (BPI). We additionally hypothesize that the mean pain score of all patients included in the study will be 5/10 before treatment.

Specific Aim #2: *To determine the impact of 10mg of loratadine by mouth daily on bone pain as assessed by the Brief Pain Inventory (BPI).*

We hypothesize that loratadine will improve pain scores by at least 2 points as measured by the BPI as compared to baseline and as compared to the placebo arm.

3. Inclusion/Exclusion Criteria

Patients eligible for this study will be between the ages of 12-99 years old.

Inclusion:

1. Diagnosis of severe congenital neutropenia, idiopathic neutropenia, or cyclic neutropenia
2. G-CSF use for at least 3 months at least 4 times per month

3. Mean bone pain of at least a 3/10 as assessed by the BPI
4. Informed consent

Exclusion:

1. Other sources of chronic pain
2. Previously tried loratadine for 7 consecutive days or more for G-CSF bone pain
3. Allergy to loratadine or any other components of the formulation
4. Chronic daily usage of antihistamine without an acceptable alternative non-antihistamine medication
5. Inability to swallow capsule medications
6. Inability to complete the survey accurately
7. Glomerular filtration rate (GFR)< 30 ml/min
8. ALT>100 U/L or AST>100 U/L
9. Currently taking any interacting drugs listed in section 12 where the recommendation is to avoid or modify loratadine administration

4. Enrollment/Randomization

This is a phase II, randomized, placebo-controlled, crossover blinded study. Patients who use G-CSF or parents/guardians of patients who use G-CSF will be contacted by phone, by email, or face-to-face when in clinic for an appointment. Informed consent will be obtained by the PI or other research personnel in person. Assent will be obtained from children who have reached the proper age, adhering to local IRB guidelines. All registration will take place at the University of Michigan in the Department of Pediatrics and Communicable Diseases and the Department of Hematology/Oncology. We expect to identify 35-125 patients who use chronic G-CSF for non-malignant indications. We expect 25-85 patients to express interest in the trial, and 20-60 patients to fit criteria for inclusion. We anticipate the recruiting to take 2 months to complete. Patients will be randomized 1:1 into placebo first or loratadine first arms (see Study Procedure).

5. Study Procedures

	Recruitment	Week 1	Week 2	Week 3	Week 4
Comprehensive metabolic panel	X[1]				
Brief Pain Inventory (BPI)		X[2]	X[1]		X[1]
Loratadine or Placebo			X		X

1 Only if CMP not recorded in the past 6 months
2 Day 2, 4, and 6 by modified BPI and day 7 with full BPI

Patients >= 12 years old who have severe congenital neutropenia, idiopathic neutropenia, or cyclic neutropenia and have used G-CSF for more than 3 months at least 4 times a month will be identified and contacted. If patients are interested in enrolling in the study, a screening questionnaire will be administered eliciting answers to the exclusion and inclusion criteria (see section 3.0). Patient charts will be checked to ensure that they have had a complete metabolic panel in the past 6 months. If not, they

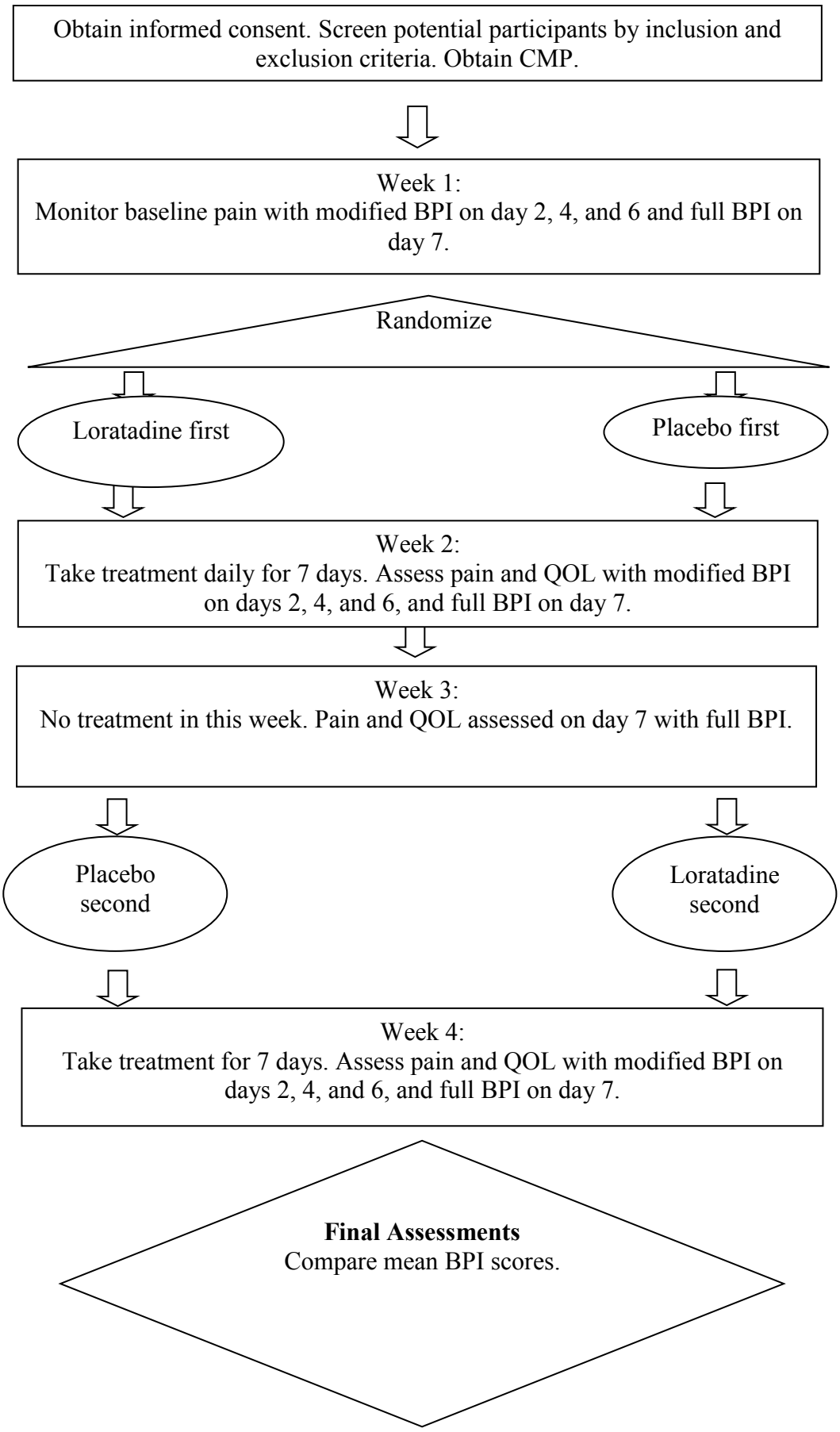
will have a blood draw and a comprehensive metabolic panel to check creatinine, AST, and ALT levels. This is part of standard of care. Additional labs will only be drawn if deemed clinically necessary or based on adverse events. If patients are eligible, they will be given an informed consent to review and sign. We expect recruitment to take 2 months. Once recruited, patients will start treatment the following Monday or on a Monday of their choosing within one month of providing informed consent.

Patients will be randomly assigned to two groups. The patients, providers, and statisticians will be blinded to which group they are a part of. Groups will have a one week observation period where baseline pain is assessed on day 2, 4, and 6 by modified BPI and on day 7 full BPI. The number of non-opioid pain medications required during the baseline week will be recorded. Patients will be asked to adhere to the same schedule, dosage, and type of pain medication throughout the next three weeks. The second week, one group will receive 10mg of loratadine once daily for 7 days and the other will receive the placebo daily. They will again be monitored with modified BPI on day 2, 4, and 6 and on day 7 full BPI. Adverse events will also be assessed during this time period.

There will then be a 7 day "wash-out" period. This wash-out period was chosen because the active metabolite of loratadine, descarboethoxyloratadine, has a mean half-life of 28 hours. It takes approximately 5 half-lives for elimination of drug from the system (28*5=140→ 5.8 days). There will be no assessment of pain or quality of life this week.

In the fourth week, the groups will switch to either placebo or the loratadine (opposite of their second week treatment). They will take this treatment by mouth for 7 days. Pain will be assessed on day 2, 4, and 6 by modified BPI, and on day 7 with full BPI. Adverse events will also be assessed during this time period. We will also follow-up via phone call 30 days after the last dose to assess for any additional adverse events.

The surveys will be administered on the online platform QuestionPro. This is an online, secure, professional survey software that will collect data from the surveys. This can be used on computers, tablets, or smartphones. Patients will be de-identified, but they will have a unique identifier that links their surveys responses. The questions come the Brief Pain Inventory (BPI). The modified BPI will only include questions 3-7 of the BPI.


Obtain informed consent. Screen potential participants by inclusion and exclusion criteria. Obtain CMP.
Week 1:
Monitor baseline pain with modified BPI on day 2, 4, and 6 and full BPI on day 7.
Randomize
Loratadine first
Placebo first
Week 2:
Take treatment daily for 7 days. Assess pain and QOL with modified BPI on days 2, 4, and 6, and full BPI on day 7.
Week 3:
No treatment in this week. Pain and QOL assessed on day 7 with full BPI.
Placebo second
Loratadine second
Week 4:
Take treatment for 7 days. Assess pain and QOL with modified BPI on days 2, 4, and 6, and full BPI on day 7.
Final Assessments
Compare mean BPI scores.

6. Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Adverse Event Definition
An adverse event (AE) is any untoward medical occurrence in a subject participating in an investigational study or protocol regardless of causality assessment. An adverse event can be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom, syndrome or disease associated with or occurring during the use of an investigational product whether or not considered related to the investigational product.

These events may be:

a. *Definitely related:* clearly associated with study drug/treatment
b. *Probably related*: likely associated with study drug/treatment
c. *Possibly related*: may be associated with study drug or other treatment
d. *Unlikely to be related*, or
e. *Definitely not related* to the study drug/treatment

For reporting purposes, an AE should be regarded as definitely or probably related to the regimen if the investigator believes that at least one of following criteria are met:

a. There is a clinically plausible time sequence between onset of the AE and the administration of the study drug or treatment.
b. There is a biologically plausible mechanism for the study drug or treatment causing or contributing to the AE.
c. The AE cannot be attributed solely to concurrent/underlying illness, other drugs, or procedures.
d. A potential alternative cause does not exist.

Serious Adverse Events (SAE): An adverse drug experience occurring at any dose that results in any of the following outcomes:

a. Death
b. A life-threatening adverse drug experience
c. Inpatient hospitalization or prolongation of existing hospitalization
d. A persistent or significant disability &/or incapacity
e. A congenital anomaly or birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. A serious adverse experience includes any experience that is fatal or immediately life threatening, results in a persistent or significant disability/incapacity, requires or prolongs in-patient hospitalization, or is a congenital anomaly, cancer, or overdose.
Other important medical events that may not result in death, not be life-threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed previously.

Expected adverse events are those listed in the protocol, drug labeling or in the study informed consent document. Unexpected events are those events that are not described in the labeling, protocol or the study informed consent. This includes adverse events for which the specificity or severity is not consistent with the description in the informed consent.

An unanticipated problem is a serious problem that has implications for the conduct of the study requiring a significant and usually safety related change in the protocol or the informed consent. Should an unanticipated problem occur during the investigation, the investigator will promptly report all unanticipated problems involves risks to human subjects or others to the IRBMED according to their guidance document.

The severity or grade of an adverse event may be measured using the following definitions:

Mild: Noticeable to the subject, but does not interfere with subject's expected daily activities, usually does not require additional therapy or intervention, dose reduction, or discontinuation of the study.

Moderate: Interferes with the subject's expected daily activities, may require some additional therapy or intervention but does not require discontinuation of the study.

Severe: Extremely limits the subject's daily activities and may require discontinuation of study therapy, and/or additional treatment or intervention to resolve.

Event Reporting
All serious adverse events (SAEs) and adverse events (AEs) will be reported to the IRB according to the IRB reporting requirements and guidelines.

7. Study Withdrawal/Discontinuation

Subjects may withdraw from the study at any time. Subjects and/or their guardians may discontinue participation for any reason and no further samples will be collected. Samples collected prior to discontinuation will still be used as part of the study unless the participant or study team request in writing for the samples to be destroyed. The study investigators may also discontinue the participation of any subject if they feel necessary. Reasons for discontinuing a subject include but are not limited to subject safety or scientific validity.

8. Statistical Considerations

Power: For 80% power at a significance level of .05, a minimum of 10 patients will enter this two-treatment crossover study. This assumes a minimal detectable difference in means of 2 and standard deviation of the difference between the two treatments for the same patient of 2 as assessed by the BPI.

Analysis: Scores will be analyzed with Chi-squared analysis. A binary yes/no designation will be given to each patient for improvement of BPI by 2 or more points during treatment arm when compared to baseline and placebo. Two sample t-test will also be used to compare means of BPI between treatment and placebo and treatment and baseline. Chi-squared analysis and two sample t-test will also be used to compare between day 2

modified BPI during treatment and placebo, between day 4 modified BPI during treatment and placebo, and between day 6 modified BPI during treatment and placebo.

Confidence Interval: Confidence intervals will be analyzed and reported from the baseline, placebo, and treatment scores of the full BPI.

Possible Pitfalls: Some patients may exit the clinical trial before completion. These patients will be included in an intention to treat analysis using analysis of the worst case scenario (no change from baseline pain and QOL scores) to fill in the missing data. Some patients may not complete all survey questions or may not complete all of the surveys even if they remain in the trial. These patients will still be included in the analysis, and missing data will be imputed with maximum likelihood method. A summary of missing response data will be included in the final report.

9. Privacy/Confidentiality Issues

Identifying data will not be published by this study. Identifying data are kept in a password protected file on an encrypted laptop as per guidelines of good clinical practice (GCP). A unique identifier will be assigned and used for each participating subject in order to link individual surveys together. The key linking the subject unique ID and personal identifying data will only be known to the local investigator and their study team. The confidentiality of records that could identify subjects will be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirements.

10. Follow-up and Record Retention

Active subject participation and enrollment is expected to last approximately 1 month. Surveys collected will be de-identified using a unique ID. Data is expected to be retained for 7 years from the completion of the study per University of Michigan record keeping guidelines.

11. Budget

Item	**Cost**
Estimated Research Pharmacy Fee	$4,435
ESTIMATED TOTAL	$4,435

If a comprehensive metabolic panel (CMP) is required, it will be billed as part of standard of care. The billing calendar fee is waived for this study.

12. Drug Information

Loratadine

- Other names for the drug: Claritin
- Description: 10 mg of intact loratadine tablets are placed into an empty capsule with 7 capsules per bottle

- Classification - type of agent: Active drug

- Mode of action: Long acting tricyclic antihistamine with selective peripheral histamine H_1-receptor antagonist activity

- Pharmacokinetics: Anti-histamine effects begins within 1-3 hours reaching a maximum at 8-12 hours and lasting in excess of 24 hours. There is no evidence of tolerance after 28 days. Times to maximum concentration after oral administration is 1.3 hours for loratadine and 2.5 hours for its major metabolite, descarboethoxyloratadine. The pharmacokinestics are independent of dose over the range of 10mg to 40mg and are not altered by duration of treatment. Loratadine is metabolized to descarboethoxyloratadine predominantly by cytochrome P450 3A4. 80% of the loratadine dose is equally distributed between urine and feces in the form of metabolic products within 10 days. The mean elimination half-lives were 8.4 hours (range 3-20 hours) for loratadine, and 28 hours (range 8.8-92 hours) for descarboethoxyloratadine. The pharmacokinetic profile or loratadine in children is similar to that of adults.

- Side effects:
  - 1% to 10%:
    - Central nervous system: Headache (adults: 8%), sedated state (adults: 8%), drowsiness (adults: 4%), fatigue (adults: 4%), nervousness (children: 4%)
    - Gastrointestinal: Xerostomia (adults: 2% to 4%), abdominal pain (children: 2%), vomiting (children: 2%), diarrhea (children: 1%)
    - Neuromuscular & skeletal: Hyperkinetic muscle activity (children: 3%)
  - Frequency not defined:
    - Dermatologic: Skin rash (adults)
    - Gastrointestinal: Gastritis (adults), nausea (adults)
    - Hypersensitivity: Hypersensitivity reaction (adults)
  - <1%, postmarketing, and/or case reports:
    - Alopecia, anaphylaxis, cough, dizziness, dry nose, hepatic insufficiency, increased appetite, palpitations, seizure, tachycardia

- Drug Interactions: The patient drug list must be screened for interacting drugs listed below, and patients excluded if the recommendation is to avoid or modify therapy.

  - AbobotulinumtoxinA: Anticholinergic Agents may enhance the anticholinergic effect of AbobotulinumtoxinA. *Risk C: Monitor therapy*

  - Acetylcholinesterase Inhibitors: May diminish the therapeutic effect of Anticholinergic Agents. Anticholinergic Agents may diminish the therapeutic effect of Acetylcholinesterase Inhibitors. *Risk C: Monitor therapy*
  - Aclidinium: May enhance the anticholinergic effect of Anticholinergic Agents. *Risk X: Avoid combination*
  - Alcohol (Ethyl): CNS Depressants may enhance the CNS depressant effect of Alcohol (Ethyl). *Risk C: Monitor therapy*
  - Alizapride: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*

- Amantadine: May enhance the anticholinergic effect of Anticholinergic Agents. *Risk C: Monitor therapy*
- Amezinium: Antihistamines may enhance the stimulatory effect of Amezinium. *Risk C: Monitor therapy*
- Amiodarone: May increase the serum concentration of Loratadine. Management: Due to reported QT interval prolongation and Torsades de Pointes with this combination, consider an alternative to loratadine when possible. *Risk D: Consider therapy modification*
- Amphetamines: May diminish the sedative effect of Antihistamines. *Risk C: Monitor therapy*
- Anticholinergic Agents: May enhance the adverse/toxic effect of other Anticholinergic Agents. *Risk C: Monitor therapy*
- Azelastine (Nasal): CNS Depressants may enhance the CNS depressant effect of Azelastine (Nasal). *Risk X: Avoid combination*
- Benzylpenicilloyl Polylysine: Antihistamines may diminish the diagnostic effect of Benzylpenicilloyl Polylysine. Management: Suspend systemic H1 antagonists for benzylpenicilloyl-polylysine skin testing and delay testing until systemic antihistaminic effects have dissipated. A histamine skin test may be used to assess persistent antihistaminic effects. *Risk D: Consider therapy modification*
- Betahistine: Antihistamines may diminish the therapeutic effect of Betahistine. *Risk C: Monitor therapy*
- Blonanserin: CNS Depressants may enhance the CNS depressant effect of Blonanserin. *Risk D: Consider therapy modification*
- Brimonidine (Topical): May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*
- Bromopride: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*
- Bromperidol: May enhance the CNS depressant effect of CNS Depressants. *Risk X: Avoid combination*
- Buprenorphine: CNS Depressants may enhance the CNS depressant effect of Buprenorphine. Management: Consider reduced doses of other CNS depressants, and avoiding such drugs in patients at high risk of buprenorphine overuse/self-injection. Initiate buprenorphine patches (Butrans brand) at 5 mcg/hr in adults when used with other CNS depressants.*Risk D: Consider therapy modification*
- Cannabidiol: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*
- Cannabis: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*
- Chloral Betaine: May enhance the adverse/toxic effect of Anticholinergic Agents. *Risk C: Monitor therapy*
- Chlormethiazole: May enhance the CNS depressant effect of CNS Depressants. Management: Monitor closely for evidence of excessive CNS depression. The chlormethiazole labeling states that an appropriately reduced dose should be used if such a combination must be used. *Risk D: Consider therapy modification*
- Chlorphenesin Carbamate: May enhance the adverse/toxic effect of CNS Depressants. *Risk C: Monitor therapy*
- Cimetropium: Anticholinergic Agents may enhance the anticholinergic effect of Cimetropium. *Risk X: Avoid combination*

- CNS Depressants: May enhance the adverse/toxic effect of other CNS Depressants. *Risk C: Monitor therapy*
- Dimethindene (Topical): May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*
- Doxylamine: May enhance the CNS depressant effect of CNS Depressants. Management: The manufacturer of Diclegis (doxylamine/pyridoxine), intended for use in pregnancy, specifically states that use with other CNS depressants is not recommended. *Risk C: Monitor therapy*
- Dronabinol: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*
- Droperidol: May enhance the CNS depressant effect of CNS Depressants. Management: Consider dose reductions of droperidol or of other CNS agents (eg, opioids, barbiturates) with concomitant use. Exceptions to this monograph are discussed in further detail in separate drug interaction monographs. *Risk D: Consider therapy modification*
- Eluxadoline: Anticholinergic Agents may enhance the constipating effect of Eluxadoline. *Risk X: Avoid combination*
- Flunitrazepam: CNS Depressants may enhance the CNS depressant effect of Flunitrazepam. *Risk D: Consider therapy modification*
- Gastrointestinal Agents (Prokinetic): Anticholinergic Agents may diminish the therapeutic effect of Gastrointestinal Agents (Prokinetic). *Risk C: Monitor therapy*
- Glucagon: Anticholinergic Agents may enhance the adverse/toxic effect of Glucagon. Specifically, the risk of gastrointestinal adverse effects may be increased. *Risk C: Monitor therapy*
- Glycopyrrolate (Oral Inhalation): Anticholinergic Agents may enhance the anticholinergic effect of Glycopyrrolate (Oral Inhalation). *Risk X: Avoid combination*
- Glycopyrronium (Topical): May enhance the anticholinergic effect of Anticholinergic Agents. *Risk X: Avoid combination*
- Hyaluronidase: Antihistamines may diminish the therapeutic effect of Hyaluronidase. Management: Patients receiving antihistamines (particularly at larger doses) may not experience the desired clinical response to standard doses of hyaluronidase. Larger doses of hyaluronidase may be required. *Risk D: Consider therapy modification*
- HYDROcodone: CNS Depressants may enhance the CNS depressant effect of HYDROcodone. Management: Avoid concomitant use of hydrocodone and benzodiazepines or other CNS depressants when possible. These agents should only be combined if alternative treatment options are inadequate. If combined, limit the dosages and duration of each drug. *Risk D: Consider therapy modification*
- HydrOXYzine: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*
- Ipratropium (Oral Inhalation): May enhance the anticholinergic effect of Anticholinergic Agents. *Risk X: Avoid combination*
- Itopride: Anticholinergic Agents may diminish the therapeutic effect of Itopride. *Risk C: Monitor therapy*
- Kava Kava: May enhance the adverse/toxic effect of CNS Depressants. *Risk C: Monitor therapy*
- Levosulpiride: Anticholinergic Agents may diminish the therapeutic effect of Levosulpiride. *Risk X: Avoid combination*

- Lofexidine: May enhance the CNS depressant effect of CNS Depressants. Management: Drugs listed as exceptions to this monograph are discussed in further detail in separate drug interaction monographs. *Risk C: Monitor therapy*
- Lumacaftor: May decrease the serum concentration of P-glycoprotein/ABCB1 Substrates. Lumacaftor may increase the serum concentration of P-glycoprotein/ABCB1 Substrates. *Risk C: Monitor therapy*
- Magnesium Sulfate: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*
- Methotrimeprazine: CNS Depressants may enhance the CNS depressant effect of Methotrimeprazine. Methotrimeprazine may enhance the CNS depressant effect of CNS Depressants. Management: Reduce adult dose of CNS depressant agents by 50% with initiation of concomitant methotrimeprazine therapy. Further CNS depressant dosage adjustments should be initiated only after clinically effective methotrimeprazine dose is established. *Risk D: Consider therapy modification*
- MetyroSINE: CNS Depressants may enhance the sedative effect of MetyroSINE. *Risk C: Monitor therapy*
- Mianserin: May enhance the anticholinergic effect of Anticholinergic Agents. *Risk C: Monitor therapy*
- Minocycline: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*
- Mirabegron: Anticholinergic Agents may enhance the adverse/toxic effect of Mirabegron. *Risk C: Monitor therapy*
- Mirtazapine: CNS Depressants may enhance the CNS depressant effect of Mirtazapine. *Risk C: Monitor therapy*
- Nabilone: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*
- Nitroglycerin: Anticholinergic Agents may decrease the absorption of Nitroglycerin. Specifically, anticholinergic agents may decrease the dissolution of sublingual nitroglycerin tablets, possibly impairing or slowing nitroglycerin absorption. *Risk C: Monitor therapy*
- OnabotulinumtoxinA: Anticholinergic Agents may enhance the anticholinergic effect of OnabotulinumtoxinA. *Risk C: Monitor therapy*
- Opioid Analgesics: CNS Depressants may enhance the CNS depressant effect of Opioid Analgesics. Management: Avoid concomitant use of opioid analgesics and benzodiazepines or other CNS depressants when possible. These agents should only be combined if alternative treatment options are inadequate. If combined, limit the dosages and duration of each drug. *Risk D: Consider therapy modification*
- Orphenadrine: CNS Depressants may enhance the CNS depressant effect of Orphenadrine. *Risk X: Avoid combination*
- Oxatomide: May enhance the anticholinergic effect of Anticholinergic Agents. *Risk X: Avoid combination*
- Oxomemazine: May enhance the CNS depressant effect of CNS Depressants. *Risk X: Avoid combination*
- OxyCODONE: CNS Depressants may enhance the CNS depressant effect of OxyCODONE. Management: Avoid concomitant use of oxycodone and benzodiazepines or other CNS depressants when possible. These agents should only be combined if alternative treatment options are inadequate. If combined,

limit the dosages and duration of each drug. *Risk D: Consider therapy modification*

- Paraldehyde: CNS Depressants may enhance the CNS depressant effect of Paraldehyde. *Risk X: Avoid combination*
- Perampanel: May enhance the CNS depressant effect of CNS Depressants. Management: Patients taking perampanel with any other drug that has CNS depressant activities should avoid complex and high-risk activities, particularly those such as driving that require alertness and coordination, until they have experience using the combination. *Risk D: Consider therapy modification*
- P-glycoprotein/ABCB1 Inducers: May decrease the serum concentration of P-glycoprotein/ABCB1 Substrates. P-glycoprotein inducers may also further limit the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*
- P-glycoprotein/ABCB1 Inhibitors: May increase the serum concentration of P-glycoprotein/ABCB1 Substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). *Risk C: Monitor therapy*
- Piribedil: CNS Depressants may enhance the CNS depressant effect of Piribedil. *Risk C: Monitor therapy*
- Pitolisant: Antihistamines may diminish the therapeutic effect of Pitolisant. *Risk C: Monitor therapy*
- Potassium Chloride: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Chloride. Management: Patients on drugs with substantial anticholinergic effects should avoid using any solid oral dosage form of potassium chloride. *Risk X: Avoid combination*
- Potassium Citrate: Anticholinergic Agents may enhance the ulcerogenic effect of Potassium Citrate. *Risk X: Avoid combination*
- Pramipexole: CNS Depressants may enhance the sedative effect of Pramipexole. *Risk C: Monitor therapy*
- Pramlintide: May enhance the anticholinergic effect of Anticholinergic Agents. These effects are specific to the GI tract.*Risk D: Consider therapy modification*
- Ramosetron: Anticholinergic Agents may enhance the constipating effect of Ramosetron. *Risk C: Monitor therapy*
- Ranolazine: May increase the serum concentration of P-glycoprotein/ABCB1 Substrates. *Risk C: Monitor therapy*
- Revefenacin: Anticholinergic Agents may enhance the anticholinergic effect of Revefenacin. *Risk X: Avoid combination*
- RimabotulinumtoxinB: Anticholinergic Agents may enhance the anticholinergic effect of RimabotulinumtoxinB. *Risk C: Monitor therapy*
- ROPINIRole: CNS Depressants may enhance the sedative effect of ROPINIRole. *Risk C: Monitor therapy*
- Rotigotine: CNS Depressants may enhance the sedative effect of Rotigotine. *Risk C: Monitor therapy*
- Rufinamide: May enhance the adverse/toxic effect of CNS Depressants. Specifically, sleepiness and dizziness may be enhanced. *Risk C: Monitor therapy*
- Secretin: Anticholinergic Agents may diminish the therapeutic effect of Secretin. Management: Avoid concomitant use of anticholinergic agents and secretin.

Discontinue anticholinergic agents at least 5 half-lives prior to administration of secretin. *Risk D: Consider therapy modification*

- Selective Serotonin Reuptake Inhibitors: CNS Depressants may enhance the adverse/toxic effect of Selective Serotonin Reuptake Inhibitors. Specifically, the risk of psychomotor impairment may be enhanced. *Risk C: Monitor therapy*
- Sodium Oxybate: May enhance the CNS depressant effect of CNS Depressants. Management: Consider alternatives to combined use. When combined use is needed, consider minimizing doses of one or more drugs. Use of sodium oxybate with alcohol or sedative hypnotics is contraindicated. *Risk D: Consider therapy modification*
- Suvorexant: CNS Depressants may enhance the CNS depressant effect of Suvorexant. Management: Dose reduction of suvorexant and/or any other CNS depressant may be necessary. Use of suvorexant with alcohol is not recommended, and the use of suvorexant with any other drug to treat insomnia is not recommended. *Risk D: Consider therapy modification*
- Tapentadol: May enhance the CNS depressant effect of CNS Depressants. Management: Avoid concomitant use of tapentadol and benzodiazepines or other CNS depressants when possible. These agents should only be combined if alternative treatment options are inadequate. If combined, limit the dosages and duration of each drug. *Risk D: Consider therapy modification*
- Tetrahydrocannabinol: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*
- Tetrahydrocannabinol and Cannabidiol: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*
- Thalidomide: CNS Depressants may enhance the CNS depressant effect of Thalidomide. *Risk X: Avoid combination*
- Thiazide and Thiazide-Like Diuretics: Anticholinergic Agents may increase the serum concentration of Thiazide and Thiazide-Like Diuretics. *Risk C: Monitor therapy*
- Tiotropium: Anticholinergic Agents may enhance the anticholinergic effect of Tiotropium. *Risk X: Avoid combination*
- Topiramate: Anticholinergic Agents may enhance the adverse/toxic effect of Topiramate. *Risk C: Monitor therapy*
- Trimeprazine: May enhance the CNS depressant effect of CNS Depressants. *Risk C: Monitor therapy*
- Umeclidinium: May enhance the anticholinergic effect of Anticholinergic Agents. *Risk X: Avoid combination*
- Zolpidem: CNS Depressants may enhance the CNS depressant effect of Zolpidem. Management: Reduce the Intermezzo brand sublingual zolpidem adult dose to 1.75 mg for men who are also receiving other CNS depressants. No such dose change is recommended for women. Avoid use with other CNS depressants at bedtime; avoid use with alcohol. *Risk D: Consider therapy modification*

- Storage and stability: Store between 20-25°C. Loratadine must be stored in a secure, limited access area.

- Preparation and Dispensing: Repackaging into prescription bottles is allowed. Active loratadine is dispensed in a bottle of 7 units of 10mg loratadine blinded capsules. The subjects are required to be blinded if they are receiving loratadine or placebo. 10

mg of intact loratadine will be placed into an empty capsule with 7 capsules per bottle by the research pharmacy in order to visually appear identical to the placebo capsules.

- Administration: Food does not impact the AUC of the active metabolite of loratadine, descarboethoxyloratadine, or the peak metabolite concentration. Therefore, the capsules can be taken with or without food. A dose should be taken at the same time every day +/- 4 hours. If a dose is missed by more than 12 hours, do not take the missed dose and continue to take the next dose as scheduled. The study team should be informed when there are missed doses. Compliance will be assessed with pill counts and a questionnaire at the end of the 7-day arm.

- Availability**:** Loratadine is commercially available. This drug will be free of charge to all study participants, and it will be purchased using study funds. Under no circumstance will the study medication, loratadine, be used other than as directed by the protocol.

- Return and Retention of Study Drug: Unused drug or empty bottles should be returned to the research pharmacy to be destroyed on site per the institution standard operating procedure for drug destruction. This destruction will be documented on the drug accountability logs.

- Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the investigational drug loratadine. The drug accountability records will capture drug receipt, drug dispensing, drug return and final disposition.

Placebo

- Description: Placebo is a lactose filler covered by a capsule with 7 capsules per bottle

- Side effects: There are no expected side effects from a placebo

- Storage and stability: Store between 20-25°C. Placebo capsules must be stored in a secure, limited access area.

- Preparation and Dispensing Placebo is a lactose filler covered by a capsule. The subjects are required to be blinded to if they are receiving loratadine or placebo. The placebo capsules visually appear identical to the capsules the loratadine pills are placed in.

- Administration: Capsules can be taken with or without food. A dose should be taken at the same time every day +/- 4 hours. If a dose is missed by more than 12 hours, do not take the missed dose and continue to take the next dose as scheduled. The study team should be informed when there are missed doses. Compliance will be assessed with pill counts and a questionnaire at the end of the 7-day arm.

- Availability**:** The placebo are lactose fillers placed in a capsule, and these will be

prepared by the Research Pharmacy and provided free of charge to all study participants.

- Return and Retention of Study Drug: Unused placebo or empty bottles should be returned to the research pharmacy to be destroyed on site per the institution standard operating procedure for drug destruction. This destruction will be documented on the drug accountability logs.

References

1. Lambertini M, Del Mastro L, Bellodi A, Pronzato P: **The five "Ws" for bone pain due to the administration of granulocyte-colony stimulating factors (G-CSFs)**. *Crit Rev Oncol Hematol* 2014, **89**(1):112-128.
2. Pawloski PA, Larsen M, Thoresen A, Giordana MD: **Pegfilgrastim use and bone pain: a cohort study of community-based cancer patients**. *J Oncol Pharm Pract* 2016, **22**(3):423-429.
3. Xu H, Gong Q, Vogl FD, Reiner M, Page JH: **Risk factors for bone pain among patients with cancer receiving myelosuppressive chemotherapy and pegfilgrastim**. *Support Care Cancer* 2016, **24**(2):723-730.
4. Kroger N, Renges H, Sonnenberg S, Kruger W, Gutensohn K, Dielschneider T, Cortes-Dericks L, Zander AR: **Stem cell mobilisation with 16 microg/kg vs 10 microg/kg of G-CSF for allogeneic transplantation in healthy donors**. *Bone Marrow Transplant* 2002, **29**(9):727-730.
5. Martinez C, Urbano-Ispizua A, Marin P, Merino A, Rovira M, Carreras E, Montserrat E: **Efficacy and toxicity of a high-dose G-CSF schedule for peripheral blood progenitor cell mobilization in healthy donors**. *Bone Marrow Transplant* 1999, **24**(12):1273-1278.
6. Arslan O, Moog R: **Mobilization of peripheral blood stem cells**. *Transfus Apher Sci* 2007, **37**(2):179-185.
7. Cesaro S, Marson P, Gazzola MV, De Silvestro G, Destro R, Pillon M, Calore E, Messina C, Zanesco L: **The use of cytokine-stimulated healthy donors in allogeneic stem cell transplantation**. *Haematologica* 2002, **87**(8 Suppl):35-41.
8. Liu C, Ma X, Jiang X, Wilson SJ, Hofstra CL, Blevitt J, Pyati J, Li X, Chai W, Carruthers N *et al*: **Cloning and pharmacological characterization of a fourth histamine receptor (H(4)) expressed in bone marrow**. *Mol Pharmacol* 2001, **59**(3):420-426.
9. Schweizerhof M, Stosser S, Kurejova M, Njoo C, Gangadharan V, Agarwal N, Schmelz M, Bali KK, Michalski CW, Brugger S *et al*: **Hematopoietic colony-stimulating factors mediate tumor-nerve interactions and bone cancer pain**. *Nat Med* 2009, **15**(7):802-807.
10. Stosser S, Schweizerhof M, Kuner R: **Hematopoietic colony-stimulating factors: new players in tumor-nerve interactions**. *J Mol Med (Berl)* 2011, **89**(4):321-329.
11. Kirshner JJ, McDonald MC, 3rd, Kruter F, Guinigundo AS, Vanni L, Maxwell CL, Reiner M, Upchurch TE, Garcia J, Morrow PK: **NOLAN: a randomized, phase 2 study to estimate the effect of prophylactic naproxen or loratadine vs no prophylactic treatment on bone pain in patients with early-stage breast cancer receiving chemotherapy and pegfilgrastim**. *Support Care Cancer* 2018, **26**(4):1323-1334.
12. Moukharskaya J, Abrams DM, Ashikaga T, Khan F, Schwartz J, Wilson K, Verschraegen C, Openshaw T, Valentine J, Eneman J *et al*: **Randomized phase II study of loratadine for the prevention of bone pain caused by pegfilgrastim**. *Support Care Cancer* 2016, **24**(7):3085-3093.

13. Sciences WFUH: **Evaluation of Loratadine for G-CSF Induced Bone Pain in Patients With Hematologic Malignancies**. In. Clinicaltrials.gov; 2018.
14. Romeo C, Li Q, Copeland L: **Severe pegfilgrastim-induced bone pain completely alleviated with loratadine: A case report**. *J Oncol Pharm Pract* 2015, **21**(4):301-304.
15. Moore K, Haroz R: **When Hydromorphone Is Not Working, Try Loratadine: An Emergency Department Case of Loratadine as Abortive Therapy for Severe Pegfilgrastim-Induced Bone Pain**. *J Emerg Med* 2017, **52**(2):e29-e31.