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(54) Titre : PREPARATION INJECTABLE LIQUIDE DE PAMIDRONATE DISODIQUE

(54) Title: LIQUID INJECTABLE FORMULATION OF DISODIUM PAMIDRONATE

(57) **Abrégé/Abstract:**

The present invention relates to an improved injectable ready to use preparation of pamidronate salts, methods for its manufacture and uses of the solution of the invention in the manufacture of pharmaceutical compositions for the treatment of diseases selected from the group of tumour-induced hypercalcaemia, Paget's disease, osteoporosis, bone metastases, or breast cancer. The ready to use solution comprises a physiologically acceptable alkaline salt which is water soluble and a physiologically acceptable aqueous solvent having a concentration of between 0.1 and 100 mg/mL which has not been reconstituted from a lyophilizate, wherein the solution is provided in a sealed non-reactive container.

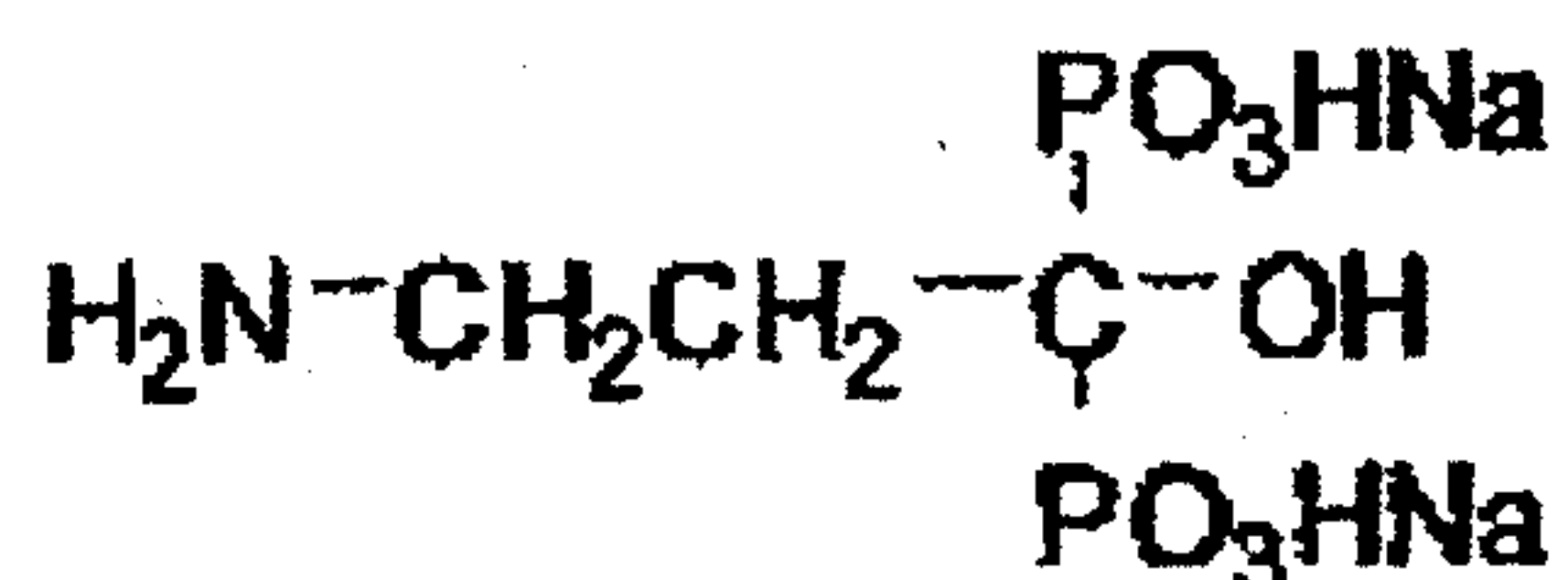
Abstract

The present invention relates to an improved injectable ready to use preparation of pamidronate salts, methods for its manufacture and uses of the solution of the invention in the manufacture of pharmaceutical compositions for the treatment of diseases selected from the group of tumour-induced hypercalcaemia, Paget's disease, osteoporosis, bone metastases, or breast cancer. The ready to use solution comprises a physiologically acceptable alkaline salt which is water soluble and a physiologically acceptable aqueous solvent having a concentration of between 0.1 and 100 mg/mL which has not been reconstituted from a lyophilizate, wherein the solution is provided in a sealed non-reactive container.

LIQUID INJECTABLE FORMULATION OF DISODIUM PAMIDRONATE

Field of the Invention

The present invention relates to an improved injectable ready to use
5 preparation of pamidronate salts of the formula given by



Background of the Invention

3-amino-1-hydroxypropane-1,1-diphosphonate disodium, the disodium
salt of pamidronic acid, is a well-known compound useful as a bone resorption
10 inhibitor. Also known as pamidronate, pamidronate disodium or disodium
pamidronate, the compound is part of the therapeutic class of compounds called
bisphosphonates. Bisphosphonates used as inhibitors of bone resorption all
contain two phosphonate groups attached to a single carbon atom, forming a "P-
C-P" structure. The bisphosphonates are therefore stable analogues of naturally
15 occurring pyrophosphate-containing compounds, which now helps to explain
their intracellular as well as their extracellular modes of action. The mode of
action of bisphosphonates was originally ascribed to physico-chemical effects
on hydroxyapatite crystals, a major inorganic component of bone, but it has
gradually become clear that cellular effects must also be involved.
20 Bisphosphonates inhibit bone resorption by being selectively taken up and
adsorbing to mineral surfaces in bone, where they interfere with the action of
osteoclasts. It is likely that bisphosphonates are internalized by osteoclasts and
interfere with specific biochemical processes and induce apoptosis.

Several bisphosphonates including etidronate, clodronate, pamidronate,
25 alendronate, and risedronate are established as effective treatments in clinical
disorders such as Paget's disease of bone, hypercalcaemia of a malignancy, and

bone metastases. Bisphosphonates are also now well established as successful antiresorptive agents for the prevention and treatment of osteoporosis. Additional indications include the reduction of bone pain associated with certain illnesses and to treat bone loss due to breast cancer.

5 U.S. Patents 4,711,880 and 4,639,338 to Stahl et al. disclose the preparation of the crystalline pentahydrate form of disodium pamidronate from pamidronic acid. A heated aqueous suspension of pamidronic acid is partially neutralized with aqueous sodium hydroxide (NaOH) to pH 7 to 7.5. Crystallization is then initiated and the disodium pamidronate is collected by
10 filtration. The pentahydrate comprises about 24.1 to 25% water and the product is stable to storage under approximately normal ambient conditions. The commercially available formulation, AREDIA™, contains the lyophilized form of pamidronate disodium pentahydrate

Other crystalline forms of disodium pamidronate convert to the
15 pentahydrate depending upon humidity and amount of water present (Stahl et al.) resulting in varying compositions of hydrates. Accordingly, it is difficult to use preformed disodium salts of pamidronic acid (such as anhydrous or partially hydrated forms other than pentahydrate) for further processing into sterile pharmaceuticals due to the interconversion of other crystalline forms of
20 disodium pamidronate.

At present, pamidronate is usually administered intravenously, due to the poor absorption from the gastrointestinal system. Pamidronate is supplied commercially as a lyophilized powder that must be reconstituted with a pharmaceutically acceptable solvent before administration to a patient.

25 Problems associated with a lyophilized formulation include a risk of microbial contamination during reconstitution and an inability to terminally sterilize the drug product. Double handling of the drug is required, as the lyophilized drug is first required to be reconstituted and then administered. Additionally, time is needed to dissolve the powder and prolonged shaking may
30 be required.

Pamidronate in a liquid formulation has been shown to be unstable/reactive during long-term storage (Canadian patent application 2,141,964). In addition, current guidelines for storage of reconstituted solutions state that the solution should not be kept for more than 24 hours.

5 One answer to the stability problem is proposed in Canadian patent application 2,141,964, which discloses injection solutions that are stable when stored in glass packaging, where the pH of the injection and solution is about 3.0 to 4.5 and polyethylene glycols are used to stabilize the solution. However, this formulation contains ingredients that are unnecessary for therapeutic
10 purposes, and the process to prepare the formulation requires several steps, such as pH adjustment.

Another liquid formulation of disodium pamidronate is disclosed in U.S. 6,160,165 to Shinal. This formulation is prepared by making a stirred slurry of pamidronic acid in water (pamidronic acid is not soluble in water); adding an
15 aqueous solution of sodium hydroxide to the slurry in an about 2:1 molar ratio of sodium hydroxide to pamidronic acid to yield a solution having visual clarity. The solution is packaged in a sealed container to yield a liquid dosage form of pamidronate. No data is given on its stability. No information is provided on sterilization of the solution to yield a pharmaceutically acceptable product. The
20 patent further discloses a lyophilized form of pamidronate, made by the steps above, filtering the solution and freezing and lyophilizing the filtered solution to yield amorphous, essentially anhydrous disodium pamidronate. This process has the disadvantage of a number of manufacturing steps. Additionally, the liquid composition cannot be stored for long periods of time as reaction of the
25 pamidronate with polyvalent cations will occur when stored in glass vials.

Assuring sterility of the injection solution is always a concern for a manufacturer. Reconstitution introduces the risk of microbial contamination. Although the preferred approach to assurance of sterility of a solution, or the gold standard, is terminal steam sterilization through autoclaving, sterile
30 filtration is used when the compound or formulation is subject to lyophilization

or is heat sensitive. (Drugs Directorate Guideline, Chemistry and Manufacturing: New Drugs 1990, Health and Welfare Canada).

Ready-to-use solutions of disodium pamidronate, provided in a sealed container, have not been commonly available. Accordingly, there is a need for
5 a stable, ready to use liquid injectable formulation that can be stored at room temperature and does not require reconstitution. There is a need for a solution that can be terminally sterilized. There is also a need for a simplified process for making a stable liquid formulation of disodium pamidronate that does not require pH adjustment nor any expensive freeze drying step.

10 Summary of the Invention

It is an object of the present invention to provide a storage stable, ready to use solution containing a pharmaceutically acceptable water-soluble alkaline salt of pamidronate as well as a process for its manufacture. In a preferred
15 embodiment, the pharmaceutically acceptable water soluble alkaline salt is the disodium salt.

According to an aspect of the invention, there is provided an injectable, sterile, ready to use, pyrogen-free pamidronate solution comprising a physiologically acceptable water soluble alkaline salt and a physiologically acceptable aqueous solvent having a concentration of between 0.1 and 100
20 mg/mL which has not been reconstituted from a lyophilizate wherein the solution is provided in a sealed non-reactive container.

According to an aspect of the present invention, there is provided a process for producing a sterile, injectable, pyrogen-free, ready-to-use pamidronate solution comprising (1) adding pamidronic acid to an aqueous
25 solvent wherein the aqueous solvent contains sodium hydroxide, potassium hydroxide, or water soluble organic amines and (2) sterilizing the solution.

Preferably, sodium hydroxide is mixed with pamidronic acid in a 2 to 1 molar ratio in an aqueous solvent to make pamidronate disodium. In a preferred

embodiment, the solution is stored in plastic vials, with non-reactive stoppers such as Teflon™ coated/faced stoppers.

The invention provides for use of the solution to treat diseases selected from the group of tumour-induced hypercalcemia, Paget's disease, osteoporosis,
5 bone metastases, and breast cancer.

Detailed Description of the Invention

Any physiologically acceptable alkaline salt that is water-soluble may be used for preparing the solution of the invention. Preferred salts are sodium and potassium. The disodium salt is the most preferred salt.

10 In a preferred embodiment, aqueous sodium hydroxide is added to a non-reactive mixing tank such as a polypropylene tank. Pamidronic acid is mixed with sodium hydroxide, in a 1:2 molar ratio, in an aqueous environment. Any aqueous solvent that is physiologically acceptable in which pamidronate remains soluble may be used. The solution of the invention may also contain
15 one or more additional components such as a preservative, a co-solubilizing agent, or any other desired agent. Suitable solvents include those that have acceptable particulate counts, such as water, or physiological saline. Tonicity adjustment agents in an amount that does not cause precipitation may be added, such as sodium chloride, dextrose, lactose, mannitol and the like.

20 Optionally, preservatives suitable for a physiological administration such as hydroxybenzoic acid esters, chlorobutanol and benzyl alcohol may be added. Although pH adjustment is not necessary for stability purposes, optionally, the pH may be adjusted within the range of from 6 to 10 using any known method of pH adjustment.

25 The concentration of the solution may be anywhere from 0.1 mg/mL to 100 mg/mL, preferably from 1 to 25 mg/mL and most preferably between 3 to 9 mg/mL.

The resulting solution may be filtered to remove particulate matter, and then is filled into non-reactive packaging. "Non-reactive", when used herein means that the packaging material must not contain multivalent metal cations that can react with the pamidronate entity. The preferred packaging material is plastic such as polypropylene, polyolefin, cycloolefin, polycarbonate, ABS
5 resin, polyethylene, or PVC.

Preferably the containers are vials with non-reactive stoppers. Preferred stoppers are Teflon™ coated/faced. Silicone rubber stoppers or other non-reactive stoppers are contemplated. Also within the scope of the present
10 invention is the use of non-reactive intravenous bags, and non-reactive ampoules, such as zirconium ampoules or form seal ampoules.

Sterility of the product may be assured through making the product in aseptic conditions, or other methods for sterilization may be used. An advantage of the present invention is the ability to use terminal sterilization processes such as autoclaving. "Terminal sterilization", when used herein,
15 means steam sterilization by autoclaving using a process validated to deliver a minimum end of exposure F_0 of 8 minutes and a maximum F_0 of 15 minutes. The solution may be autoclaved according to methods known in the art. Alternatively, the solution may be passed through a sterilizing filter, such
20 as a 0.22 micron Supor DCF capsule.

The solutions of the invention are characterized by good stability. Solutions have been found to be stable for long periods at room temperature. This is illustrated in the examples which follow.

The pharmaceutical compositions of the present invention are useful for
25 treating any bone resorption disorders or conditions. Examples of these indications are tumor-induced hypercalcemia, conditions associated with increased osteoclast activity, predominantly lytic bone metastases and multiple myeloma as well as symptomatic Paget's disease of bone.

The composition of the present invention is designed to be diluted and administered as a slow intravenous infusion. The injectable solutions of the invention are administered according to a variety of possible dose schedules. Suitable dose schedules are for example 90 mg as a 2 hour infusion in 250 ml
5 infusion solution or a maximum of 90 mg in 500 ml over 4 hours for patients with multiple myeloma or tumor induced hypercalcemia. The total dose for a treatment course may be given as a single infusion, or in multiple infusions spread over 2-4 consecutive days. The maximum dose should be 90 mg. The recommended total dose of pamidronate disodium injection for a treatment
10 course for Paget's disease of the bone is 180-210 mg either administered as 6 doses of 30 mg once a week or 3 doses of 60 mg every second week following initiation with a 30 mg dose.

In light of the present disclosure, those skilled in the art will readily appreciate other methods and applications of the methods of the present
15 invention.

The examples below are non-limiting and are merely representative of various aspects and features of the present invention.

With reference to the examples, the stability testing on the injectable solution was carried out by means of high performance liquid chromatography
20 (HPLC) at the following experimental conditions:

<u>HPLC Assay Method</u>	
Column(s)/ temperature (if other than ambient):	Waters IC Pak Anion HR, 4.6 x 75 mm HPLC column or equivalent / 35°C
Mobile phase (specify gradient program if applicable):	0.0165% formic acid, pH = 3.5
Detector /wavelength (if applicable):	Refractive Index
Flow rate:	1.0 mL / min.
Injection volume:	10 µL

Example 1: Pamidronate disodium solution 9mg/mL

Composition	For 1 Vial (10 mL)	per mL
Pamidronic acid	75.82 mg	7.582 mg
Sodium hydroxide NF	25.81 mg	2.581 mg
Mannitol USP	375.0 mg	37.5 mg
Water for injection USP	Q.S. to 10 mL volume	Q.S. to 1 mL volume
Phosphoric acid NF	10% for pH adjustment	10% for pH adjustment

- 5 Water for injection USP was collected in a clean, non-reacting polypropylene mixing tank at room temperature. Sodium hydroxide NF was

added to the water and mixed thoroughly until completely dissolved.
Pamidronic acid was then added and mixed until completely dissolved.
Mannitol USP was then added and completely dissolved. The pH was then
adjusted to between 6.4 and 6.6 with 10% phosphoric acid. Water for injection
5 USP was added to the final required volume.

The solution was filtered through a sterilizing 0.22 micron Supor-DCF
filter. Volumes of 10 ml of the solution were distributed into plastic vials. The
vials were then closed with TeflonTM-faced/coated rubber stoppers and sealed,
and steam sterilized by autoclaving using a using a process validated to deliver
10 a minimum end of exposure Fo of 8 minutes and a maximum Fo of 15 minutes.

The stability of the solutions in the vials was tested after accelerated
testing at 40° C (accelerated stability controls) and at room temperature for a
minimum of 6 months. The stability data obtained, using HPLC for the
determination of potency are reported in the following Tables 1 and 2.

15

TABLE 1**INITIAL VALUES****Concentration: 3 mg/mL****Relative % Assay: 100.0 %****pH: 6.62**

Time (months)	TEMPERATURE			
	25°±2°C / 60%±5% RH		40°±2°C / 75%±5% RH	
	Conc. mg/mL	Rel. % Assay	Conc. mg/mL	Rel. % Assay
0	3.00	100.0	3.00	100.0
1	---	---	3.02	100.7
2	---	---	3.00	100.0
3	3.01	100.3	3.01	100.3
6	2.99	99.7	---	---

TABLE 2**INITIAL VALUES**

(a) Concentration: 9 mg/mL

Relative % Assay: 100.0%

pH: 6.49

Time (months)	TEMPERATURE			
	25°±2°C / 60%±5% RH		40°±2°C / 75%±5% RH	
	Conc. mg/mL	Rel. % Assay	Conc. mg/mL	Rel. % Assay
0	8.66	96.2	8.66	96.2
1	---	---	8.71	96.8
2	---	---	8.67	96.3
3	8.70	96.7	8.71	96.8
6	8.71	96.8	---	---

While the present invention has been described with reference to what are presently considered to be the preferred examples, it is to be understood that the invention is not limited to the disclosed examples. To the contrary, the invention is intended to cover various modifications and equivalent arrangements included within the spirit and scope of the appended claims.

The embodiments of the invention in which an exclusive privilege or property is claimed are defined as follows:

1. An injectable, sterile, ready to use, pyrogen-free pamidronate solution comprising a physiologically acceptable alkaline salt which is water soluble and a physiologically acceptable aqueous solvent having a concentration of between 0.1 and 100 mg/mL which has not been reconstituted from a lyophilizate, wherein the solution is provided in a sealed non-reactive container.
2. A solution according to claim 1, wherein the physiologically acceptable alkaline salt is selected from the group of sodium and potassium salts.
3. A solution according to claim 1, wherein the physiologically acceptable alkaline salt is the disodium salt.
4. A solution according to any one of claims 1 to 3, wherein the concentration is between 3 and 9 mg/mL.
5. A solution according to any one of claims 1 to 4, wherein the sealed container is made of a material selected from the group of polypropylene, polyolefin, cycloolefin, polycarbonate, ABS resin, polyethylene, and PVC.
6. A solution according to claim 5, wherein the sealed container additionally comprises a non-reactive stopper.
7. A solution according to claim 6, wherein the stopper is TeflonTM-coated/faced.
8. A solution according to any one of claims 1 to 7 which also contains one or more additional components selected from a co-solubilizing agent, a preservative and a tonicity adjustment agent.
9. A solution according to any one of claims 1 to 8 which also contains dextrose, lactose or mannitol as a tonicity adjustment agent.
10. A solution according to any one of claims 1 to 9 having a pH of from 6.3 to 6.7.

11. A solution according to any one of claims 1 to 10 where the solvent is selected from the group consisting of water, and physiological saline.
12. A process for producing a sterile, injectable, pyrogen-free, ready-to-use pamidronate solution comprising: (i) adding pamidronic acid to an aqueous solvent wherein the aqueous solvent is selected from the group of sodium hydroxide, potassium hydroxide and a water soluble organic amine; and (ii) sterilizing the solution.
13. A process according to claim 12, wherein the aqueous solvent is sodium hydroxide.
14. A process according to claim 13, where the molar ratio of sodium hydroxide to pamidronic acid is 2:1.
15. A process according to claim 14 which further comprises placing the solution in a sealed non-reactive container.
16. A process according to claim 15, wherein the sealed container is a plastic vial.
17. A process according to claim 16, wherein the sealed container additionally comprises a non-reactive stopper.
18. A process according to claim 17, wherein the stopper is TeflonTM-coated/faced.
19. A process according to claim 15, wherein the sealed container is selected from the group of a form seal ampoule and plastic bag used for preparation or administration of intravenous solution.
20. A process according to any one of claims 12 to 19 which additionally comprises the step of adjusting the pH of the solution to 6 to 10.
21. A process according to claim 20 wherein the pH of the solution is adjusted to 6.3 to 6.7.

22. A process according to any one of claims 12 to 20 which comprises the additional step of adding a component selected from the group of co-solubilizing agents, preservatives and tonicity adjustment agents.
23. A process according to claim 12, which comprises the additional step of adding a physiologically acceptable solvent.
24. A process according to any one of claims 12 to 22 wherein the step of sterilization comprises passing the solution through a sterilizing filter.
25. A process according to any one of claims 12 to 23 wherein the step of sterilization comprises terminal sterilization of the sealed containers.
26. The solution made by the process of any one of claims 12 to 25.
27. Use of the solution of any one of claims 1 to 11 for the manufacture of a pharmaceutical composition for the treatment of diseases selected from the group of tumour-induced hypercalcaemia, Paget's disease, osteoporosis, bone metastases, and breast cancer.