Important Prescribing Information

Subject: Temporary importation of 8.4% Sodium Bicarbonate Injection to address drug shortage issues

May 23, 2017

Dear Healthcare Professional,

Due to the current critical shortage of Sodium Bicarbonate Injection, USP in the United States (US) market, Athenex Pharmaceutical Division, LLC (Athenex) is coordinating with the U.S. Food and Drug Administration (FDA) to increase the availability of Sodium Bicarbonate Injection. Athenex has initiated temporary importation of another manufacturer’s 8.4% Sodium Bicarbonate Injection (1 mEq/mL) into the U.S. market. This product is manufactured and marketed in Australia by Phebra Pty Ltd (Phebra).

At this time, no other entity except Athenex Pharmaceutical Division, LLC is authorized by the FDA to import or distribute Phebra’s 8.4% Sodium Bicarbonate Injection, (1 mEq/mL), 10 mL and 100mL vials, in the United States. FDA has not approved Phebra’s 8.4% Sodium Bicarbonate Injection but does not object to its importation into the United States. Effective immediately, and during this temporary period, Athenex will offer the following presentation of Sodium Bicarbonate Injection:

Sodium Bicarbonate Injection, 8.4% (1mEq/mL), 10mL per vial, 10 vials per carton
Ingredients: sodium bicarbonate, water for injection, disodium edetate and sodium hydroxide (pH adjustment)
Marketing Authorization Number in Australia is: 131067

Phebra’s Sodium Bicarbonate Injection contains the same active ingredient, Sodium Bicarbonate, in the same strength and concentration, 8.4% (1 mEq/mL) as the U.S. registered Sodium Bicarbonate Injection, USP by Pfizer’s subsidiary, Hospira. However, it is important to note that Phebra’s Sodium Bicarbonate Injection (1 mEq/mL), is provided only in a Single Use 10 mL and 100mL vials, whereas Hospira’s product is provided in 50 mL single-dose vials and syringes. Any unused portion of Phebra’s Sodium Bicarbonate Injection (1 mEq/mL) should be discarded after a single use.

There are some key differences in the labeling between the U.S. marketed Sodium Bicarbonate Injection and the imported product (please see the product comparison table at the end of this letter):
Sodium Bicarbonate Injection is only available by prescription in the U.S. Please refer to the FDA-approved package insert at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=077394 for the full prescribing information for 8.4% Sodium Bicarbonate Injection (1 mEq/mL).

**The barcode may not register accurately on the U.S. scanning systems.** Institutions should manually input the product into their systems and confirm that barcode systems do not provide incorrect information when the product is scanned. Alternative procedures should be followed to assure that the correct drug product is being used and administered to individual patients.

**To order or if you have questions** about Phebra’s 8.4% Sodium Bicarbonate Injection, (1 mEq/mL), 10 mL and 100mL vials, please contact Athenex’s Customer Service by phone at 1-855-273-0154.

**To report adverse events or quality problems** among patients who have received Phebra’s 8.4% Sodium Bicarbonate Injection, (1 mEq/mL), 10 mL and 100mL vials, please contact Athenex’s Medical Affairs by phone at 1-855-273-0154. Adverse events or quality problems may also be reported to FDA’s MedWatch Adverse Reporting Program either online, by regular mail or fax:

- Complete and submit the report Online: [www.fda.gov/medwatch/report.htm](http://www.fda.gov/medwatch/report.htm)
- **Regular Mail or Fax**: Download form [www.fda.gov/MedWatch/getforms.htm](http://www.fda.gov/MedWatch/getforms.htm) or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178 (1-800-332-0178)

If you have any questions about the information contained in this letter or the safe and effective use of Phebra’s 8.4% Sodium Bicarbonate Injection, (1 mEq/mL), 10 mL and 100mL vials, please contact Athenex’s Medical Affairs at 1-855-273-0154.

Sincerely,

Thomas J. Moutvic
Vice President, Regulatory Affairs
Athenex Pharmaceutical Division, LLC
### Molecular formula
- **Pfizer**: NaHCO₃
- **Phebra**: NaHCO₃

### Available Concentration
- **Pfizer**: 84 mg/mL and 75 mg/mL
- **Phebra**: 840 mg/10 mL

### Route of administration
- **Pfizer**: Intravenous
- **Phebra**: Intravenous

### Unit of Use
- **Pfizer**: 8.4% and 7.5% in Ansyr II prefilled syringe, 50 mL vial
- **Phebra**: 840 mg/10 mL (8.4%) sodium bicarbonate in water for injections (10 mL glass vial and 100 mL glass vial)

### Dosage
- **Pfizer**: Single dose
- **Phebra**: Single use in one patient on one occasion only.

### pH
- **Pfizer**: 0.17 (0 to 8.5)
- **Phebra**: 0.0 to 8.5

### Claims
- **Pfizer**: Sterile, nonpyrogenic, hypertonic solution, system alkalizer, contains no bacteriostat, no antimicrobial agent added
- **Phebra**: Sterile solution, contains no antimicrobial agent

### Equivalency
- **Pfizer**: Water for injection, USP
- **Phebra**: Water for injections

### excursion for pH adjustment
- **Pfizer**: N/A
- **Phebra**: Blood plasma edetate and sodium hydride (for pH adjustment)

### Pharmacology (what it does)
- **Pfizer**: Increases plasma bicarbonate buffers excess hydrogen ion concentration raises blood pH reverses clinical manifestations of acidosis
- **Phebra**: Systemic alkalizing agent that: increases plasma bicarbonate buffer excess hydrogen ion concentration raises blood pH reverses clinical manifestations of acidosis

### Pharmacology (in water)
- **Pfizer**: Dissociates in water to provide sodium and bicarbonate ions. Sodium (Na) is the principal cation of the extracellular fluid and plays a large part in the therapy of fluid and electrolyte disturbances. Bicarbonate (HCO₃⁻) is a normal constituent of body fluids and the normal plasma level ranges from 24 to 31 mEq/L.
- **Phebra**: Dissociates in water to provide sodium and bicarbonate ions. Sodium is the principal cation of the extracellular fluid and plays a large part in the therapy of fluid and electrolyte disturbances. Bicarbonate is a normal constituent of body fluids and the normal plasma level ranges from 24 to 31 mmol/L.

### Pharmacology (kidney function)
- **Pfizer**: Plasma concentration is regulated by the kidney through acidification of the urine when there is a deficit or by alkalization of the urine when there is an excess. Bicarbonate anion is considered "labile" since at a proper concentration of hydrogen ion [H⁺] it may be converted to carboxic acid (H₂CO₃) and thence to its volatile form, carbon dioxide (CO₂) excreted by the lung. Normally a ratio of 1:20 (carboxic acid:bicarbonate) is present in the extracellular fluid. In a healthy adult with normal kidney function, practically all the glomerular filtered bicarbonate ion is reabsorbed; less than 1% is excreted in the urine.
- **Phebra**: Acid-base homeostasis exerts a major influence on protein function, thereby critically affecting tissue and organ performance. Systemic arterial pH is maintained by extracellular and intracellular chemical buffering together with respiratory and renal regulatory mechanisms. The control of arterial carbon dioxide (CO₂) tension (PaCO₂) by the central nervous system and respiratory systems and the control of the plasma bicarbonate by the kidneys stabilize the arterial pH by excretion or retention of acid or alkali. Under most circumstances, CO₂ production and excretion are matched, and the usual steady-state PaCO₂ is maintained at 40 mmHg. The kidneys regulate plasma HCO₃⁻ through three main processes: (1) "reabsorption" of filtered HCO₃⁻, (2) formation of titratable acid, and (3) excretion of NH₄⁺ in the urine. The kidney filters approximately 4000 mmol of HCO₃⁻ per day. To reabsorb the filtered load of HCO₃⁻, the renal tubules must therefore secrete 4000 mmol of hydrogen ions. Between 80% and 90% of HCO₃⁻ is reabsorbed in the proximal tubule. The distal nephron reabsorbs the remainder and secretes protons, as generated from metabolism, to defend systemic pH. While this quantity of protons, 40 to 60 mmol/d, is small, it must be secreted to prevent chronic positive H⁺ balance and metabolic acidosis. This quantity of secreted protons is represented in the urine as titratable acid and NH₄⁺. Metabolic acidosis in the face of normal renal function increases NH₄⁺ production and excretion. NH₄⁺ production and excretion are impaired in chronic renal failure, hyperkalaemia, and renal tubular acidosis. The management of serious acid-base disorders always demands precise diagnosis and treatment of the underlying disease, and in certain circumstances, it requires steps to combat the deviation in systemic acidosis itself. Administration of sodium bicarbonate will increase the plasma HCO₃⁻ concentration and help restore the plasma pH within the normal range (pH 7.35-7.45). Changes in acid-base balance also stimulate compensatory ion-exchange mechanisms. When the extracellular hydrogen ion concentration increases, as in acidosis, there is a redistribution of potassium ions from intracellular to extracellular fluid. Administration of sodium bicarbonate can cause a redistribution of potassium ions into cells in patients with acidosis, by increasing the plasma pH. The urinary pH will be increased by sodium bicarbonate in patients with normal renal function. Alkalinising the urine can increase the solubility of certain weak acids, and can increase the ionization and urinary excretion of lipid-soluble organic acids (e.g. phenobarbital, salicylates).

### Indications and Usage
- **Pfizer**: Sodium Bicarbonate Injection, USP is indicated in the treatment of metabolic acidosis which may occur in severe renal disease, uncontrolled diabetes, circulatory insufficiency due to shock or severe dehydration, extracorporeal circulation of blood, cardiac arrest and severe primary lactic acidosis. Sodium bicarbonate is further indicated in the treatment of certain drug intoxications, including barbiturates (where dissociation of the barbiturate-protein complex is desired), in poisoning by salicylates or methyl alcohol and in hemolytic reactions requiring alkalization of the urine to diminish nephrotoxicity of hemoglobin and its breakdown products. Sodium bicarbonate also is indicated in severe diarrhea which is often accompanied by a significant loss of bicarbonate. Treatment of metabolic acidosis should, if possible, be superimposed on measures designed to control the basic cause of the acidosis – e.g., insulin in uncomplicated diabetes, blood volume repletion in shock. But since an appreciable time interval may elapse before all of the ancillary effects are brought about, bicarbonate therapy is indicated to minimize risks inherent to the acidosis itself. Vigorous bicarbonate therapy is required in any form of metabolic acidosis where a rapid increase in plasma total CO₂ content is crucial – e.g., cardiac arrest, circulatory insufficiency due to shock or severe dehydration, and in severe primary lactic acidosis or severe diabetic acidosis.
- **Phebra**: Sodium Bicarbonate Injection is indicated as an alkalising agent in the treatment of metabolic acidosis which may occur in many conditions including diabetes, starvation, hepatitis, cardiac arrest, shock, severe dehydration, renal insufficiency, severe diarrhoea, Addison's disease or administration of acidifying salts (e.g. excessive sodium chloride, calcium chloride, ammonium chloride). Sodium Bicarbonate Injection is also used to increase urinary pH in order to increase the solubility of certain weak acids (e.g. cystine, sulphanamides, uric acid) and in the treatment of certain intoxications (e.g. ethanol, phenobarbital, salicylates, lithium) to decrease renal absorption of the drug or to correct acidosis.

### Contraindications
- **Pfizer**: Sodium Bicarbonate Injection, USP is contraindicated in patients who are losing chloride by vomiting or from continuous gastrointestinal suction, and in patients receiving diuretics known to produce a hypochloremic alkalosis.
- **Phebra**: Sodium Bicarbonate Injection is contraindicated in patients with renal failure, respiratory or metabolic alkalosis, hypocloremia or chloride depletion, hyperventilation, hyperventilation, oedema, congestive heart failure, eclampsia, aldosteronism, a history of urinary calculi and consistent potassium depletion or hypercalcaemia. It is also generally contraindicated in patients with excessive chloride loss from vomiting or continuous gastrointestinal suctioning and in patients at risk of developing diuretic-induced hypochloremic alkalosis.
Geriatric

Solutions containing sodium ions should be used with great care, if at all, in patients with congestive heart failure, severe renal insufficiency and in clinical states in which there exists edema with sodium retention. In patients with diminished renal function, administration of solutions containing sodium ions may result in sodium retention. The intravenous administration of these solutions can cause fluid and/or solute overloading resulting in dilution of serum electrolyte concentrations, overhydration, congested states or pulmonary edema. Extravascular infiltration should be avoided. The potentially large loads of sodium given with bicarbonate require that caution be exercised in the use of sodium bicarbonate in patients with congestive heart failure or other edematous or sodiumretaining states, as well as in patients with oliguria or anuria.

Special Population (CHF and renal insufficiency)

Use in patients with congestive heart failure or renal insufficiency

Sodium retention and oedema may occur during sodium bicarbonate therapy, especially when the drug is given in large doses or to patients with renal insufficiency, congestive heart failure or those predisposed to sodium retention and oedema. Sodium and water overload may result in hyperkalaemia and hypocalcemia, sodium and water retention, and cardiac pulmonary resuscitation when excessive doses of sodium bicarbonate are administered. Serum potassium may decrease during sodium bicarbonate therapy leading to hyperkalaemia. Sodium bicarbonate should be used with extreme caution in patients with congestive heart failure or other edematosus or sodium-retaining conditions; in patients with renal insufficiency, especially those with severe insufficiency such as oligura or anuria; and in patients receiving corticosteroids or corticotropin, since each gram of sodium bicarbonate contains 12mEq of sodium.
ADVERSE REACTIONS
Overly aggressive therapy with Sodium Bicarbonate (Injection, USP) can result in metabolic alkalosis (associated with muscular twichings, irritability, and tetany) and hypernatremia. Inadvertent extravasation of intravenously administered hypertonic solutions of sodium bicarbonate have been reported to cause chemical cellulitis because of their alkalinity, with tissue necrosis, ulceration or sloughing at the site of infiltration. Prompt elevation of the part, warmth and local injection of lidocaine or hyaluronidase are recommended to reduce the likelihood of tissue sloughing from extravasated IV solutions.

ADVERSE EFFECTS
Metabolic alkalosis and/or hypokalaemia may ensue as a result of prolonged use or over correction of the bicarbonate deficit, especially in patients with impaired renal function. (See OVERDOSAGE)
Metabolic alkalosis may be accompanied by compensatory hyperventilation, paradoxical acidosis of the cerebrospinal fluid, severe hypokalaemia, hyperirritability or tetany. Hyperventilation has been reported with sodium bicarbonate use, especially in patients with renal disease. Hypernatremia has also been associated with sodium bicarbonate use. Accidental extravasation of hypertonic solutions of sodium bicarbonate has been reported to cause chemical cellulitis, with tissue necrosis, ulceration or sloughing at the site of infiltration. Prompt elevation of the part, warmth and local injection of lidocaine or hyaluronidase are recommended to prevent sloughing of extravasated intravenous infusions. Hyperirritability or tetany may occur, caused by rapid shifts of free ionised calcium due to serum protein alterations arising from the pH changes. Cerebral oedema has occurred with sodium bicarbonate use and a possibility of intracranial haemorrhage exists. Hypercapnia has occurred in patients receiving sodium bicarbonate and with fixed ventilation.

OVERDOSAGE
Alkalosis is a result of overdose.
Symptoms of Overdose
Symptoms include mood changes, tiredness, slow breathing, muscle weakness and irregular heartbeat. Muscle hyperactivity, twitching and tetany may develop, especially in hypocalcaemic patients.
Metabolic alkalosis, which may be accompanied by compensatory hyperventilation, paradoxical acidosis of the cerebrospinal fluid, severe hypernatremia, hyperirritability or tetany. Treatment of Overdose
Treatment of metabolic alkalosis associated with bicarbonate overdose consists mainly of appropriate correction of fluid and electrolyte balance. Replacement of calcium, chloride and potassium ions may be of particular importance. The bicarbonate should be stepped down and the patient managed according to the degree of alkalosis present. To control the symptoms of alkalosis the patient should re-breathe expired air. Sodium chloride injection 0.9% may be given intravenously; potassium chloride also may be indicated if there is hypokalaemia. Calcium gluconate may be used to control hyperirritability and tetany which can occur in severe alkalosis. Ammonium chloride may also be indicated as an acidifying agent in severe cases (except in patients with pre-existing hepatic disease). Treatment of hypernatraemia usually requires water replacement; restricted sodium intake and oral water may be sufficient. If more severe, glucose 5% may be administered by slow intravenous infusion. If total body sodium is too high, loop diuretics combined with an infusion of glucose 5% and potassium supplementation may be necessary.

DOSEAGE AND ADMINISTRATION
Sodium Bicarbonate Injection, USP is administered by the intravenous route. In cardiac arrest, a rapid intravenous dose of one to two 50 mL syringes (44.6 to 50 mL) may be given initially and continued at a rate of 50 mL (44.6 to 50 mL) every 5 to 10 minutes if necessary (as indicated by arterial blood pressure and blood gas monitoring) to reverse the acidosis. Caution should be observed in emergencies where very rapid infusion of large quantities of bicarbonate is indicated. Bicarbonate solutions are hypertonic and may produce an undesirable rise in plasma sodium concentration in the process of correcting the metabolic acidosis. In cardiac arrest, however, the risks from acidosis exceed those of hypernatraemia.

DOSEAGE AND ADMINISTRATION (continued)
In less urgent forms of metabolic acidosis, Sodium Bicarbonate Injection, USP may be added to other intravenous fluids. The amount of bicarbonate to be given to older children and adults over a four-to-eight-hour period is approximately 2 to 5 mmol/kg of body weight – depending upon the severity of the acidosis as judged by the lowering of total CO2 content, blood pH and clinical condition of the patient. In metabolic acidosis associated with shock, therapy should be monitored by measuring blood gases, plasma osmolality, arterial blood lactate, hemodynamics and cardiac output. Bicarbonate therapy should always be planned in a stepwise fashion since the degree of response from a given dose is not precisely predictable. Initially an infusion of 2 to 5 mmol/kg body weight over a period of 4 to 8 hours will produce a measurable improvement in the abnormal acid-base status of the blood. The next step of therapy is dependent upon the clinical response of the patient. If severe symptoms have abated, then the frequency of administration and the size of the dose may be reduced. In general, it is wise to attempt full correction of a low total CO2 content during the first 24 hours of therapy, since this may be accompanied by an unrecognized alkalosis because of a delay in the readjustment of ventilation to normal. Owing to this lag, the achievement of total CO2 content of about 20 mmol/liter at the end of the first day of therapy will usually be associated with a normal blood pH. Further modification of the acidosis to completely normal values usually occurs in the presence of normal kidney function when and if the cause of the acidosis can be controlled. Values for total CO2 which are brought to normal or above normal within the first day of therapy are very likely to be associated with grossly alkaline values for blood pH, with ensuing undesired side effects. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Intravenous Infusion - In less urgent forms of metabolic acidosis, Sodium Bicarbonate Injection may be added to 5% glucose for intravenous infusion. (See COMPATIBILITY / INCOMPATIBILITY) Sodium Bicarbonate 8.4% Injection can be diluted with 5% glucose injection or 0.9% sodium chloride injection. To reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2°C–8°C for not more than 24 hours. Sodium Bicarbonate Injection for intravenous infusion is preferably administered in a large vein, over 4 to 8 hours in mild conditions of metabolic acidosis. The amount of bicarbonate to be given as intravenous infusion to older children and adults over a 4 to 8 hour period is approximately 2 to 5 mmol/kg of bodyweight, depending upon the severity of the acidosis as judged by the lowering of the total CO2 content, blood pH and clinical condition of the patient. Standard texts and institutional protocols specific to the underlying disorder should be consulted for calculation of individual dosage. Bicarbonate therapy should always be planned in a stepwise fashion since the degree of response from a given dose is not precisely predictable. In general, it is wise to attempt full correction of a low total CO2 content during the first 24 hours of therapy, since this may be accompanied by an unrecognized alkalosis because of a delay in the readjustment of ventilation to normal.

Storage
Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature.] Store below 30°C. Do not freeze.

Pfizer

Phebra