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INTRODUCTION

Disease Overview

Leukemia and lymphomas are two of the main types of childhood cancers. Acute lymphocytic leukemia (ALL) is primarily a familiar childhood (onset under age 15 years) leukemia that accounts for approximately 57% of childhood leukemias. 1 There are approximately 6,000 cases of ALL in the United States annually.2 In recent years, the prognosis for children with ALL has improved dramatically. Before effective antileukemic therapy, most children with ALL only survived several months after diagnosis. In the past, although children with ALL were able to achieve prolonged remission with systemic chemotherapy, electrolyte/subsequent relapse due to meningeal leukemia was a frequent problem. These relapses were believed to be due to the inability of many systemic chemotherapeutic agents to cross the blood-brain barrier and gain access to the central nervous system. It was presumed that the bone marrow was reinfiltrated by leukemic cells residing in the central nervous system. Most patients died of systemic leukemia as a result of bone marrow relapse. The overall effect was a significantly graver prognosis with very few, if any, long-term remissions among patients with meningeal leukemia.

Attempts to minimize the incidence of meningeal relapse with the use of prophylactic central nervous system therapy were made. After a short time, intrathecal methotrexate sodium and concomitant cranial irradiation became the standard form of prophylactic central nervous system therapy. The subsequent development of two or three drug treatment regimens administered intrathecally has allowed physicians to avoid cranial irradiation in the majority of children. In children with ALL, the 5 year relative survival rate (percent of persons living ⍰5 years after diagnosis) has increased to 85% in pediatrics, and 68% overall (NCI).

Current treatment involves the use of systemic and intrathecally-administered chemotherapeutic treatment regiments (i.e., methotrexate sodium or cytarabine). Unfortunately, the intrathecal administration of chemotherapeutic treatment regimens is associated with acute neurotoxicity, some of which can be life-threatening or even fatal. The most common neurotoxicity is chemical arachnoiditis. Chemical arachnoiditis is an acute, self-limiting Syndrome that may begin within hours after the intrathecal injection. Chemical arachnoiditis has been observed to occur. It is characterized by meningism (pseudomeningitis), stiff neck, nausea, vomiting, headache, fever, leg pain, and cerebrospinal fluid pleocytosis (increase of Leukocytes in the cerebrospinal fluid). Less commonly, severe motor dysfunction of the brain and spinal cord may be observed are characterized by seizures, acute respiratory failure, paraplegia, quadriplegia, cerebella dysfunction, and cranial nerve palsies (some of which may not be reversible).

Elliotts B™ Solution

Elliotts BTM Solution (buffered intrathecal dextrose injection) is a buffered electrolyte/dextrose solution developed more than 50 years ago to mimic the pH, osmolarity, and composition of cerebrospinal fluid (see Table 1). From 1976 to 1992, the National Cancer Institute (NCI) of the National Institutes of Health (NIH) provided Elliotts B Solution for use in the NCI-sponsored clinical trials utilizing intrathecal methotrexate sodium. Elliotts B Solution is now commercially available.

Elliotts B Solution functions as a diluent for intrathecally-administered methotrexate sodium and cytarabine.

The buffer capacity of Elliotts B Solution was sufficient to affect the final pH of both acidic (cytarabine) and basic (methotrexate sodium) formulations in a non-clinical evaluation performed using sodium chloride injection and sterile water for injection.[4] The approximate buffer capacity of Elliotts B Solution is 1.1×10^{2} equivalents when the challenge solution is 0.01 N HCl and 7.8×10^{3} equivalents when the challenge solution is 0.01 N NaOH.[4]

CHEMISTRY

Description

Elliotts B Solution is a buffered electrolytes/dextrose Solution developed to mimic the pH, osmolarity, and Composition of cerebrospinal fluid (see Table 1). Elliotts B Solution is a sterile, nonpyrogenic, isotonic Solution containing no bacteriostatic preservatives. The pH of Elliotts B Solution is 6.0-7.5, and the Osmolarity is 288 mOsmo/liter (calculated).

Each 10 mL of Elliotts B Solution contains:

Sodium Chloride, USP
Sodium Bicarbonate, USP
Dextrose, USP
injection.4 Magnesium Sulfate ⍰ 7 H_2O, USP
Potassium Chloride, USP
Calcium Chloride ⍰ 2 H_2O,
USPSodium Phosphate,
Dibasic ⍰ 7 H_2O USP
Water for Injection, USP

Buffer Capacity

Elliotts B Solution provides a buffered electrolyte/dextrose solution for use as a diluent for the intrathecal administration of methotrexate sodium and cytarabine. Elliotts B Solution is comparable to cerebrospinal fluid In pH, electrolyte composition, glucose content, and osmolarity (see Table 1).

The buffer capacity of Elliotts B Solution was sufficient to affect the final pH of both acidic (cytarabine) and basic (methotrexate sodium) formulations in a non-clinical evaluation performed using sodium chloride injection and sterile water for

Table 1. pH, Osmolarity, and Composition of Cerebrospinal Fluid: Comparison with Elliotts B Solution and Sodium Chloride Injection, USP

Solution	pH	Osmolarity (mOsm/kg)	Na+ (mEq/L)	K+ (mEq/L)	Ca++ (mEq/L)	Mg++ (mEq/L)	HCO_3- (mEq/L)	Cl- (mEq/L)	Phos-phorus (mg/dL)	Glucose (mg/dL)
Cerebrospinal Fluid	7.31	281	117-137	2.3-4.6	2.3	2.2	22.9	113-127	1.2-2.1	45-80
Elliotts B Solution	6.0-7.5	288	149	4.0	2.7	2.4	22.6	132	2.3	80
Sodium Chloride Injection, USP	6.0-6.4	290	154	0	0	0	0	154	0	0

Indication and Usage

Elliotts B Solution is indicated as a diluent for the intrathecal administration of methotrexate sodium and the cytarabine for the prevention or treatment of meningeal leukemia or lymphocytic lymphoma.

Indication and Usage and Administration

Preparation and Administration Precautions
See product labeling for methotrexate sodium and cytarabine.
Elliotts B Solution is a diluent for the cytotoxic anti-cancer

A sterile filter-needle should be used to withdraw the contents of the ampule.

Intrathecal drug products should be inspected visually For particulate matter and discoloration prior to administration.

Solution is intended for intrathecal administration only. Elliotts B Solution does not contain antibacterial preservatives and introduction of contaminated solutions into the cerebrospinal fluid may have extremely serious consequences. Therefore, administration of intrathecal solutions should be accomplished as soon as possible after preparation.

DILUENT COMPALIBITY

Introduction

Compatibility studies with methotrexate sodium and cytarabine indicate these drugs are physical compatible with Elliotts B Solution.

Compatibility Studies

The following studies provide information on the stability of methotrexate sodium and cytarabine in Elliotts B Solution at various doses and by a variety of methodologies.

Stability of cytarabine and methotrexate sodium admixtures:

A study was conducted to evaluate the stability of methotrexate sodium and cytarabine in four diluents: 0.9% sodium chloride injection, lactated Ringer's Injection, 5% dextrose injection, and Elliotts B Solution.[5] Solutions were prepared with two concentrations of each drug similar to those administered intrathecally. Admixtures were prepared in Elliotts B Solution, 0.9% sodium chloride injection, 5% dextrose injection, and Lactated Ringer's injection. Solutions were filtered and kept in a disposable syringe in a 25℃ water bath for 24 hours. A high-performance liquid chromatographic (HPLC) assay capable of separating each drug and their respective degradation products was developed and and validated.

Methotrexate sodium and cytarabine were stable in all fluids studied for 24 hours at room temperature (25℃). Alterations in stability related to diluents or drug concentration combinations were not evident. No precipitation was observed in the admixture of these during eight hours at room temperature (25℃).

Admixtures of each drug in the four diluents tested were demonstrated to be stable for at least 10 hours Medical

at room temperature (25℃). However, intrathecal administration of such admixtures within several hours of preparation is encouraged since none contains antibacterial preservatives.

agents, methotrexate sodium and cytarabine. Elliotts B Care should be exercised in the handling and preparation of infusion solutions with these products. (See product labeling for methotrexate and cytarabine.)

Contraindications

None known.

Physical and chemical stability of methotrexate sodium and cytarabine in Elliotts B Solution:

A study was conducted to evaluate the physical and Chemical stabilities of methotrexate sodium 2 mg/mL and cytarabine 3 mg/3mL in Elliotts B Solution.[6]

The physical stability of each drug in Elliotts B Solution was assessed by visual examination and the measurement of turbidity, particle size, and particle content of duplicate samples of each combination. Visual examinations were performed immediately after admixture and after 12, 24, and 48 hours. Triplicate test solutions of each drug in Elliotts B Solution in each packaging system at both 4℃ and 23℃ were evaluated for chemical stability. Portions of the solution were removed immediately after after preparation and after 12, 24, and 48 hours of storage. The samples were analyzed for drug content using duplicate HPLC determinations. Stability was defined As retaining ≥90% of the initial drug concentration for each of the test drugs.

No precipitation was observed and all of the test solutions appeared to be clear to the unaided eye. There was no increase in particle count determined electronically over 48 hours of storage in any of the samples. The methotrexate sodium and cytarabine samples were reasonably stable in Elliotts B Solution throughout the 48 hour study period.

Methotrexate sodium 2 mg/mL and cytarabine 3 mg/mL In Elliotts B Solution packaged in glass vials and plastic syringes were demonstrated to be physically and chemically stable for at least 48 hours at both 4℃ and 23℃.

Other Agents

There are numerous ongoing studies with intrathecal and other IV agents with Elliotts B Solution. Lukare

is interesting in exploring additional study possibilities for furthering the usage and understanding of Elliotts B Solution's potential as a diluent with the goal of improving patient outcomes.

Table 2. Approximate Buffer Capacity of Elliotts B Solution:Comparison with Sodium Chloride Injection, USP

Vehicle	Challenge Solution	
	0.01 N HCl	0.01 N NaOH
Elliotts B Solution	1.1×10^{-2}	7.8×10^{-3}
Sodium Chloride Injection, USP	5.3×10^{-4}	$4.4 - 10^{-4}$

Table 3. pH of Methotrexate Sodium and Cytarabine in Elliotts B Solution:Comparison with Sodium Chloride Injection, USP

Vehicle	Methotrexate Sodium (1) *		Methotrexate Sodium (2)*		Methotrexate Sodium (3)* 1 mg/mL	Cytarabine 2.5/mg/mL
	2.5mg/mL	1 mg/mL	2.5mg/mL	1 mg/mL		
Elliotts B Solution	7.2	7.3	7.3	7.4	7.8	7.3
Sodium Chloride Injection, USP	7.6	7.3	8.2	8.0	8.5	5.3

**The following preparations of methotrexate sodium were diluted to 2.5 mg/mL and/or 1 mg/mL; (1) lyophilized, preservative-free methotrexate sodium,50 mg/vial; (2) a 25 mg/mL sterile solution (Lederle); and (3) a 2.5 mg/mL solution (Lederle).*

SAFETY

Safety

The safety data clearly demonstrate that Elliotts B Solution does not increase adverse reactions over those of the chemotherapeutic drug used, the disease itself, or other diluents.[3.7–10] Elliotts B Solution has been demonstrated to be well tolerated as a diluent for the intrathecal injection of methotrexate sodium and cytarabine.[3.7–10]

Adverse Reactions

Adverse reactions may occur with any given intrathecal injection due to the chemotherapy or the technique of intrathecal administration. (See product labeling for methotrexate sodium and cytarabine.)

Preservative-free methotrexate sodium and cytarabine should be used to minimize adverse reaction due to preservatives.

If an adverse reaction does occur, discontinue the administration, evaluate the patient, institute appropriate therapeutic countermeasures and if, possible, save the remainder of the unused solution(s) for examination.

Warnings

Intrathecal administration of drugs such as methotrexate sodium and cytarabine should be performed by personnel skilled in the technique of lumbar puncture under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents. The labeling for methotrexate sodium and cytarabine should be consulted.

Precautions

General

Particular attention should be taken to assume the maintenance of sterile technique throughout the procedure. (See DOSAGE AND ADMINISTRATION.)

Carcinogenesis, Mutagenesis, Impairment of Fertility

No standard mutagenicity or carcinogenicity studies Have been conducted with Elliotts B Solution.

Usage in Pregnancy

All Components of Elliotts B Solution are normal body constituents. Animal reproduction studies have not been conducted with Elliotts B Solution.

Overdosage

Elliotts B Solution is a diluent. In the event of a drug, fluid or solute overload following administration, evaluate the patient's condition, and institute appropriate corrective measurement. (See product labeling for methotrexate sodium and cytarabine.)

SUMMARY

- Elliotts B Solution is buffered electrolytes/dextrose solution for use as a diluent in the intrathecal admin istration of methotrexate sodium and cytarabine for the prevention of treatment of meningeal leukemia or lymphocytic lymphoma.

- Elliotts B Solution is comparable to cerebrospinal fluid in pH, osmolarity, electrolyte, composition, and glucose content.

- The buffer capacity of Elliotts B Solution was sufficient to affect the final pH of both acidic (cytarabine) and basic (methotrexate sodium) formulations in a non-clinical evaluation performed using sodium chloride injection and sterile water for injection.[4]

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10. Data on file.

411200

Elliotts B® Solution

(buffered intrathecal electrolyte/dextrose injection)

Rx only

411200

DESCRIPTION

Elliotts B® Solution is a sterile, nonpyrogenic, isotonic solution containing no bacteriostatic preservatives. Elliotts B Solution is a diluent for intrathecal administration of methotrexate sodium and cytarabine.

Each 10 mL of Elliotts B Solution contains:

Sodium Chloride, USP	73 mg
Sodium Bicarbonate, USP	19 mg
Dextrose, USP	8 mg
Magnesium Sulfate • $7H_2O$, USP	3 mg
Potassium Chloride, USP	3 mg
Calcium Chloride • $2H_2O$, USP	2 mg
Sodium Phosphate, dibasic • $7H_2O$, USP	2 mg
Water for Injection, USP	qs 10 mL

Concentration of Electrolytes:

Sodium	149	mEq/liter	Bicarbonate	22.6	mEq/liter
Potassium	4.0	mEq/liter	Chloride	132	mEq/liter
Calcium	2.7	mEq/liter	Sulfate	2.4	mEq/liter
Magnesium	2.4	mEq/liter	Phosphate	1.5	mEq/liter

The formulae and molecular weights of the ingredients are:

INGREDIENT	MOLECULAR FORMULA	MOLECULAR WEIGHT
Sodium Chloride	NaCl	58.44
Sodium Bicarbonate	$NaHCO_3$	84.01
Dextrose	$C_6H_{12}O_6$	180.16
Magnesium Sulfate • $7H_2O$	$Mg_2SO_4 • 7H_2O$	246.48
Potassium Chloride	KCl	74.55
Calcium Chloride • $2H_2O$	$CaCl_2 • 2H_2O$	147.01
Sodium Phosphate, dibasic • $7H_2O$	$Na_2HPO_4 • 7H_2O$	268.07

The pH of Elliotts B Solution is 6.0 - 7.5, and the osmolarity is 288 mOsmol per liter (calculated).

CLINICAL PHARMACOLOGY

Elliotts B Solution provides a buffered salt solution for use as a diluent for the intrathecal administration of methotrexate sodium and cytarabine. It has been demonstrated that Elliotts B Solution is comparable to cerebrospinal fluid in pH, electrolyte composition, glucose content, and osmolarity:

Comparison of Electrolyte Composition, pH and Nonelectrolytic Constituents of Elliotts B Solution and CSF

Solution	Na^+ mEq/L	K^+ mEq/L	Ca^{++} mEq/L	Mg^{++} mEq/L	HCO_3^- mEq/L	Cl^- mEq/L	pH	Phosphorus mg/dL	Glucose mg/dL
Cerebrospinal Fluid	117-137	2.3-4.6	2.2	2.2	22.9	113-127	7.31	1.2-2.1	45-80
Elliotts B Solution	149	4.0	2.7	2.4	22.6	132	6.0-7.5	2.3	80

The approximate buffer capacity of Elliotts B Solution is 1.1×10^{-2} equivalents when the challenge solution is 0.01 N HCl and 7.8×10^{-3} equivalents when the challenge solution is 0.01 N NaOH.[1]

Compatibility studies with methotrexate sodium and cytarabine indicate these drugs are physically compatible with Elliotts B Solution.

INDICATIONS AND USAGE

Elliotts B Solution is indicated as a diluent for the intrathecal administration of methotrexate sodium and cytarabine for the prevention or treatment of meningeal leukemia or lymphocytic lymphoma.

CONTRAINDICATIONS

None known.

WARNINGS

Intrathecal administration of drugs such as methotrexate sodium and cytarabine should be performed by personnel skilled in the technique of lumbar puncture under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents. The labeling for methotrexate sodium and cytarabine should be consulted.

PRECAUTIONS

General

Particular attention should be taken to assure the maintenance of sterile technique throughout the procedure. (See DOSAGE AND ADMINISTRATION.)

Carcinogenesis, Mutagenesis, Impairment of Fertility

No standard mutagenicity or carcinogenicity studies have been conducted with Elliotts B Solution.

Usage in Pregnancy

All components of Elliotts B Solution are normal body constituents. Animal reproduction studies have not been conducted with Elliotts B Solution.

ADVERSE REACTIONS

Adverse reactions may occur with any given intrathecal injection due to the chemotherapy or the technique of intrathecal administration. (See product labeling for methotrexate sodium and cytarabine.)

Preservative-free methotrexate sodium and cytarabine should be used to minimize adverse reactions due to preservatives.

If an adverse reaction does occur, discontinuethe administration, evaluate the patient, institute appropriate therapeutic countermeasures and, if possible, save the remainder of the unused solution(s) for examination.

DRUG ABUSE AND DEPENDENCE

There is no potential for drug abuse or drug dependence.

OVERDOSAGE

Elliotts B Solution is a diluent. In the event of a drug, fluid or solute overload following administration, evaluate the patient's condition, and institute appropriate corrective treatment. (See product labeling for methotrexate sodium and cytarabine.)

DOSAGE AND ADMINISTRATION

See product labeling for methotrexate sodium and cytarabine.

Elliotts B Solution is intended for intrathecal administration only. Elliotts B Solution does not contain antibacterial preservatives and introduction of contaminated solutions into the cerebrospinal fluid may have extremely serious consequences. Therefore, administration of intrathecal solutions should be accomplished as soon as possible after preparation.

A sterile filter-needle should be used to withdraw the contents of the ampule.

Intrathecal drug products should be inspected visually for particulate matter and discoloration prior to administration.

Preparation and Administration Precautions

Elliotts B Solution is a diluent for the cytotoxic anticancer agents, methotrexate sodium and cytarabine. Care should be exercised in the handling and preparation of infusion solutions with these products. (See product labeling for methotrexate sodium andcytarabine.)

HOW SUPPLIED

NDC	SIZE
55792-007-10	Each box contains 10 ampules each ampule contains 10 ml of product

Elliotts B Solution is available in single-use clear glass ampules, packaged 10 ampules per box.

Store at controlled room temperature, 20°-25°C (68°-77°F) [See USP].

Preservative Free. Discard unused portion. Use only if solution is clear and ampule is intact.

Distributed by: Lukare Medical, LLC
Ponte Vedra Beach, FL 32082
1-855-752-9317
www.elliottsbsolution.com

REFERENCES:

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