CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-569

PHARMACOLOGY REVIEW

PHARMACOLOGY AND TOXICOLOGY REVIEW

NDA #: 21-569

Drug Name: Sodium Chloride Injection USP 0.9%

Sponsor: Mallinckrodt, Inc./TYCO Healthcare

Indication: For use in flushing compatible intravenous administration sets and indwelling intravascular access devices

Division: Anesthetic, Critical Care and Addiction Drug Products

Reviewer: Timothy J. McGovern, Ph.D.

Regulatory Recommendation: AP

Date: July 18, 2003

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EXECUTIVE SUMMARY

1. Recommendations

1.1 Recommendation on approvability: This drug product application is approvable from a nonclinical perspective pending incorporation of the recommended changes to the product label.

1.2 Recommendation for nonclinical studies: None at this time.

1.3 Recommendations on labeling: A label review was conducted and it is detailed [redacted]

2. Summary of nonclinical findings

2.1 Brief overview of nonclinical findings: No nonclinical safety studies were performed for this submission. Sodium chloride is an endogenous compound and, when used under the directed conditions, is not expected to result in any adverse effects. The sponsor did conduct a series of biocompatibility studies for [redacted] that is a component of the previously approved syringe. The studies demonstrated no potential for adverse effects.

2.2 Pharmacologic activity: No specific studies regarding the general pharmacology or safety pharmacology of sodium chloride were conducted. Sodium Chloride Injection has no specific pharmacologic activity but is a source of water and electrolytes and has approximately the same osmotic pressure and composition of extracellular fluids.

2.3 Nonclinical safety issues relevant to clinical use: None at this time.

PHARMACOLOGY/TOXICOLOGY REVIEW

3.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-569
Review number: 1
Sequence number/date/type of submission: 000/September 30, 2002/Original NDA
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Mallinckrodt Inc./Tyco Healthcare, St. Louis, MO
Manufacturer for drug substance: Mallinckrodt, Inc., Phillipsburg, NJ

Reviewer name: Timothy J. McGovern, Ph.D.
Division name: Anesthetic, Critical Care and Addiction Drug Products
HFD #: 170
Review completion date: July 18, 2003

Drug:

Trade name: TBD
Generic name: Sodium chloride injection, 0.9% USP
Code name: 1178
Chemical name: Sodium chloride
CAS registry number: 7647-14-5
Molecular formula/molecular weight: NaCl/58.44
Structure: NA

Relevant INDs/NDAs/DMFs: Sodium chloride, either alone or in combination with other electrolytes, is listed as an active ingredient in an extensive number of approved products.

Drug class: electrolyte

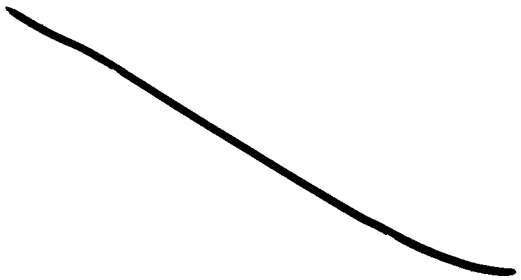
Indication: For use in flushing compatible intravenous administration sets and indwelling intravascular access devices

Clinical formulation: 0.9% NaCl in water for injection; each ml contains 9 mg NaCl, pH is 4.5 to 7.

Route of administration: intravenous

Proposed use: The packaging configurations proposed are 50 ml fill in a 50 ml syringe and a 125 ml fill in a 125 ml syringe. The proposed indication for the 50 ml syringe differs from that of the 125 ml syringe in that manual flushing is allowed. The product is to be used for flushing compatible IV administration sets and indwelling intravascular access devices.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.



Studies not reviewed within this submission: None.

This NDA is submitted as a 505(b)(2). A meeting was held with the sponsor on July 17, 2002. The sponsor was informed that it would be acceptable to provide nonclinical qualification studies, which support acceptability of the container closure components. The sponsor submitted *in vivo* and *in vitro* qualification studies relating to the syringe barrel [redacted]. Mallinckrodt utilizes the patented Ultraject syringe technology and the identical container closure components in other products that are currently approved. The [redacted] is approved for use with Optispray (NDA 19-710). The syringe tip cap and piston component composition is approved for use with OptiMARK (NDA 20-976).

3.2 PHARMACOLOGY

3.2.1 Brief summary

No specific studies regarding the general phamacology or safety pharmacology of sodium chloride were conducted. Sodium Chloride Injection has no specific pharmacologic activity but is a source of water and electrolytes and has approximately the same osmotic pressure and composition of extracellular fluids.

3.2.2 Primary pharmacodynamics

Mechanism of action: No specific studies were performed with sodium chloride. Sodium Chloride Injection has no specific pharmacologic activity but is a source of water and electrolytes and has approximately the same osmotic pressure and composition of extracellular fluids.

Drug activity related to proposed indication: Sodium Chloride Injection is a source of water and electrolytes and has approximately the same osmotic pressure and composition of extracellular fluids.

3.2.3 Secondary pharmacodynamics

Studies to assess the secondary pharmacodynamics of sodium chloride have not been performed and there are no known effects.

3.2.4 Safety pharmacology

Neurological effects: No studies were conducted by the sponsor to assess the neurological effects of sodium chloride. None are considered necessary for approval of this endogenous compound.

Cardiovascular effects: No studies were conducted by the sponsor to assess the cardiovascular effects of sodium chloride. None are considered necessary for approval of this endogenous compound.

Pulmonary effects: No studies were conducted by the sponsor to assess the pulmonary effects of sodium chloride. None are considered necessary for approval of this endogenous compound.

Renal effects: No studies were conducted by the sponsor to assess the renal effects of sodium chloride. None are considered necessary for approval of this endogenous compound.

Gastrointestinal effects: No studies were conducted by the sponsor to assess the gastrointestinal effects of sodium chloride. None are considered necessary for approval of this endogenous compound.

Abuse liability: No studies were conducted by the sponsor to assess the abuse liability of sodium chloride. None are considered necessary for approval of this endogenous compound.

Other: Not applicable.

3.2.5 Pharmacodynamic drug interactions

No studies to assess drug interactions were conducted by the sponsor. None are considered necessary for approval of this endogenous compound.

3.3 PHARMACOKINETICS/TOXICOKINETICS

3.3.1 Brief summary

No studies to assess the pharmacokinetic/toxicokintecs were conducted by the sponsor. None are considered necessary for approval of this endogenous compound.

3.3.2 Absorption

No studies to assess the absorption of sodium chloride were conducted by the sponsor. None are considered necessary for approval of this endogenous compound.

3.3.3 Distribution

No studies to assess the distribution of sodium chloride were conducted by the sponsor. None are considered necessary for approval of this endogenous compound.

3.3.4 Metabolism

No studies to assess the metabolism of sodium chloride were conducted by the sponsor. None are considered necessary for approval of this endogenous compound.

3.3.5 Excretion

No studies to assess the excretion of sodium chloride were conducted by the sponsor. None are considered necessary for approval of this endogenous compound.

3.3.6 Pharmacokinetic drug interactions

No studies to assess the pharmacokinetic drug interactions of sodium chloride were conducted by the sponsor. None are considered necessary for approval of this endogenous compound.

3.3.7 Tables and figures to include comparative TK summary

Not applicable.

3.4 TOXICOLOGY

3.4.1 Overall toxicology summary

General toxicology: No studies to assess the general toxicology of sodium chloride were conducted by the sponsor. None are considered necessary for approval of this endogenous compound under the conditions proposed for use. A review of the literature identified median lethal doses (LD_{50}) in rats of 3000 mg/kg, po, in rats and in mice of 2602 mg/kg, ip, and 4000 mg/kg, po.

Genetic toxicology: No studies to assess the genetic toxicology of sodium chloride were conducted by the sponsor. None are considered necessary for approval of this endogenous compound.

Carcinogenicity: No studies to assess the carcinogenicity of sodium chloride were conducted by the sponsor. None are considered necessary for approval of this endogenous compound.

Reproductive toxicology: No studies to assess the reproductive toxicology of sodium chloride were conducted by the sponsor. None are considered necessary for approval of this endogenous compound. This drug should be listed as a Category C for pregnancy due to the lack of information concerning reproductive potential.

Special toxicology: No studies to assess the special toxicology of sodium chloride were conducted by the sponsor. None are considered necessary for approval of this endogenous compound.

3.4.2 Single-dose toxicity
No studies were conducted.

3.4.3 Repeat-dose toxicity
No studies were conducted.

3.4.4 Genetic toxicology
No studies were conducted.

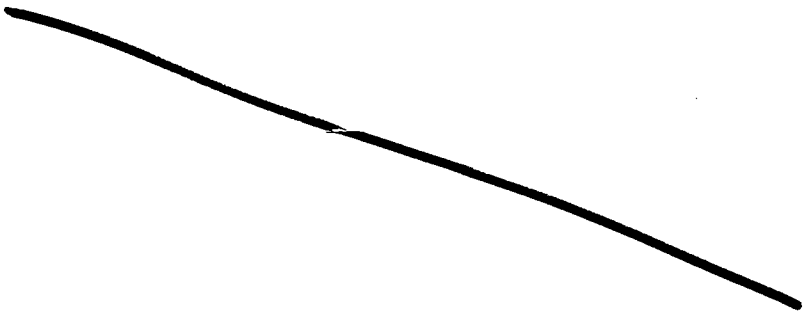
3.4.5 Carcinogenicity
No studies were conducted.

3.4.6 Reproductive and developmental toxicology
No studies were conducted.

3.4.7 Local tolerance
No studies were conducted.

3.4.8 Special toxicology studies

No studies were conducted to assess the special toxicology of sodium chloride.



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✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Pharm/Tox- 7

3.6 OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: There is extensive clinical use of 0.9% sodium chloride solutions alone or in combination with other electrolytes under the conditions of proposed use. The sponsor did not conduct any specific pharmacology or toxicology studies to support this NDA and none were requested given the endogenous nature of the compound and extensive clinical experience. The sponsor submitted a series of biocompatibility studies that were conducted to support the safety of a syringe [redacted] The studies did not identify any safety concerns and [redacted] has been used in the previously approved syringes. Thus, this drug application is approvable from a nonclinical perspective pending incorporation of the recommended changes to the product label.

Unresolved toxicology issues: None at this time.

Recommendations: This NDA application is approvable from a nonclinical perspective pending incorporation of the recommended changes to the product label.

Suggested labeling:

Sponsor's proposed labeling: The following is the sponsor's proposed labeling for the relevant portion of the Precautions section:

PRECAUTIONS

General
Do not reuse. For single patient use only. Do not use if solution is cloudy or discolored. Do not use if the syringe, piston, or tip cap are damaged in any way.

[redacted]

PREGNANCY CATEGORY C

Animal reproductive studies have not been conducted with Sodium Chloride Injection. It is also not known whether Sodium Chloride Injection can cause fetal harm when administered to a pregnant woman of can affect reproduction capacity. Sodium Chloride Injection USP 0.9% should only be given to a pregnant woman if clearly needed.

The following sections of the proposed label should be revised as follows:

The following section should be added to the Precautions section of the label just prior to the Pregnancy section:

[redacted]

The Pregnancy section should be edited as follows (the drug name should be edited once it is finalized):

PREGNANCY CATEGORY C

Animal reproduction studies have not been conducted with Sodium Chloride Injection USP 0.9%. It is also not known whether Sodium Chloride Injection USP 0.9% can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Sodium Chloride Injection USP 0.9% should be given to a pregnant woman only if clearly needed.

Signatures:

Reviewer Signature Timothy J. McGovern
Supervisory Pharmacologist, HFD-170

3.7 APPENDIX/ATTACHMENTS

None.

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/s/

Timothy McGovern
7/18/03 03:42:20 PM
PHARMACOLOGIST

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MEMORANDUM

To: NDA 21-569

From: Tim McGovern, Ph.D., Supervisory Pharmacologist, HFD-170

Subject: Revisions to the product label

Sponsor: Mallinckrodt, Inc./TYCO Healthcare

Date: JULY 22, 2003

The purpose of this memo is to update the product label text based upon a discussion of the review team. The original edits to the relevant nonclinical sections of the package insert were made in the original NDA review dated July 18, 2003.

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/s/

Timothy McGovern
7/22/03 01:44:04 PM
PHARMACOLOGIST