CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209988Orig1s000

NON-CLINICAL REVIEW(S)

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 209988, (505(b)2)
Supporting document/s:	eCTD Sequence #: 0034
Review date:	11/20/2020
Product:	Furoscix Infusor (buffered furosemide)
Indication:	For treatment of edema associated with congestive heart failure
Sponsor:	scPharmaceuticals, Inc., Lexington, MA
Review Division:	Division of Pharmacology and Toxicology (OCHEN/DPT/DCN)
Preclinical Reviewer:	Belay Tesfamariam, PhD

Introduction

The Sponsor has resubmitted an NDA 209988 in response to the complete response (CR) letter on the deficiencies of the furoscix device system. In the resubmitted application, the sponsor has replaced the original device design with an improved on-body delivery system to address the issues raised in the CR letter. Nonclinical biocompatibility testing of the post-change on-body infusor device was conducted according to the ISO 10993 for biological evaluation of medical devices. The nonclinical information on furosemide is relied on the listed drug furosemide injection (IV, IM) in the NDA 18667 to support this application for the treatment of edema associated with congestive heart failure. In this review, the sponsor's data on buffered furosemide formulation (furoscix) infused subcutaneously in rabbits are reviewed to support local tolerance.

1. Brief Discussion of Nonclinical Findings

The nonclinical studies examined local tolerability of subcutaneously infused furoscix (buffered furosemide pH 7.4) via surgically implanted catheter at the base of the neck to the caudal part of the lumbar in New Zealand White rabbits. Administration of a single 5-hour subcutaneous infusion of furoscix was well-tolerated in male and female rabbits at dosages up to 60 mg/kg and a 14-day observation period. The animals showed increased urine output indicating diuresis efficacy of subcutaneously administered furoscix. There were slight increases in red blood cell parameters (red blood cell count, hemoglobin, hematocrit), creatine kinase and urea nitrogen, and decrease in serum potassium and chloride. All values returned to the control levels during recovery period, indicating that the changes may be secondary to dehydration and electrolytes imbalance following diuresis. There were no furoscix-related changes in coagulation parameters compared to control group animals. There was no gross or microscopic evidence of local irritation at the infusion site. In the drug product, (b) (4) impurity was qualified in animal studies. Thus, subcutaneous infusion of furoscix at doses up to 60 mg/kg (HED 19.5 mg/kg) was not associated with local toxicity, which is approximately 15-fold higher than human dose of 80 mg (1.33 mg/kg).

(HED = human equivalent dose)

1.1 Recommendations

1.1.1 Approvability

Furoscix administered subcutaneously is well-tolerated. Nonclinical studies were not conducted using the new to-be-marketed furoscix infusor, and hence the approvability of the drug-device combination product will rely on the performance of the device system.

1.1.2 Nonclinical Comments

The nonclinical studies of subcutaneously infused buffered furosemide using implanted catheter did not reveal any irritation or other local reaction; however, local discomfort or irritation using the furoscix infusor device cannot be excluded.

1.1.3 Labeling

The labeling on carcinogenesis, and reproductive and developmental toxicology is updated according to new label format [section 12].

2 Drug Information

2.1 Drug

CAS registry number: 54-31-9

International nonproprietary name: Furosemide

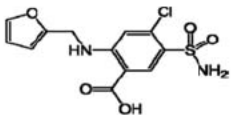
Buffered furosemide formulation: Furoscix

Chemical name: 4-chloro-N-furfuryl-5-sulfamoylanthranilic acid;
5-(aminosulfonyl)-4-chloro-2[(2-furanylmethyl)-amino]-benzoic acid

Chemical formula: $C_{12}H_{11}ClN_2O_5S$

Molecular weight: 330.75 daltons

Structure formula:



Pharmacologic class: Loop diuretic (inhibits $Na^+/K^+/2Cl^-$ cotransporter in the ascending thick loop of Henle).

Route of administration: Subcutaneous via the infusor

Drug delivery system: Furoscix on-body infusor device

2.2 Relevant INDs, NDAs, and DMFs

NDA 18667 - Reference listed drug, furosemide IV and IM injection, pH 8.3 to 9.0.
IND 118919 – Buffered furosemide subcutaneous administration, pH 7.4

2.3 Drug Formulation

Furoscix is buffered furosemide (80 mg/10 mL) with tromethamine hydrochloride (Tris HCl) to a pH of 7.4 (7.0 - 7.8) to improve tolerability during subcutaneous administration (Table 1).

Table 1: Composition of the drug product

Ingredients	Composition		Function	Quality Standard
	Quantity	Percent		
Active Substances(s)				
Furosemide	8 mg/mL	~0.8	Active ingredient	USP/Ph. Eur.
Excipients				
Tris HCl	7.88 mg/mL	~0.8	(b) (4)	Bio Excipient
Sodium Chloride	5.84 mg/mL	~0.6		USP/NF, Ph. Eur.
Hydrochloric Acid	qs to pH 7.4	-	pH adjustment	USP/NF, Ph. Eur.
Sodium Hydroxide	qs to pH 7.4	-	pH adjustment	USP/NF, Ph. Eur.
Water for Injection	qs to 1 mL	-	(b) (4)	USP/NF, Ph. Eur.

NF = National Formulary; Ph. Eur. = European Pharmacopoeia; qs =quantity sufficient

2.4 Novel Excipients

There are no novel excipients. Inactive ingredients in the formulation include sodium chloride and tromethamine (Tris HCl).

2.5 Impurities/Degradants

In the drug product, (b) (4) was identified as a degradation product. (b) (4) impurity was qualified based on a wide margin of safety data generated in three studies, including a 6-day subcutaneous toxicity study with a (b) (4) structural analog in the rabbit, a 13-week oral (diet) toxicity study (b) (4) in the rat, and a 28-day dermal toxicity study (b) (4) in the rat (Table 2). In addition, studies in transgenic mice showed that (b) (4) is non-genotoxic, and studies in the rat and rabbit showed that (b) (4) is non-teratogenic.

Table 2: Safety margin for (b) (4) at a theoretical level of 0.5%

Calculated Safety Margins for Theoretical (b) (4) Impurity Level of 0.5% Endpoint	Study/Species	Route	NOAEL (mg/kg/day)	Safety Margin*	Adjusted Safety Margin**
Systemic (Liver)	6-day rabbit study w/ (b) (4)	S.C.	(b) (4)		
Systemic (Liver)	13-week rat study (b) (4)	Oral			
Local (Dermal application site)	28-day rat study (b) (4)	Dermal			

Human daily dose of (b) (4) (mg) at 0.5% level = (b) (4) mg/kg/day)
*Safety margin = animal NOAEL in mg/kg ÷ estimated human (b) (4) dose (b) (4) mg/kg/day.
10-fold adjustment for route to route extrapolation. * (b) (4)
(b) (4); NOAEL of (b) (4) mg/kg/day = (b) (4) mg HMF/day ÷ rabbit BW of 2.5 kg.

2.6 Leachables and extractables

In the furosemide drug product, three non-volatile leachables, including (b) (4) (b) (4) were identified in the glass vial and stopper. The levels of the leachables were qualified using ICH Q3B at a specification of not-more-than 0.5%. Extractable studies performed by GC-MS identified several organic chemicals in the cartridge, but none were (b) (4) µg/device, which is below the threshold of toxicological concern (1.5 µg/day/lifetime, ICH M7).

2.7 Biocompatibility of drug-device combination product

The biocompatibility of the post-change on-body infusor delivery system are reviewed by the CDRH under the International Standard ISO 10993 for biological evaluation of medical devices.

2.8 Proposed Clinical Dosing

Subcutaneous infusion of furoscix 80 mg over 5 hours, administered as 30 mg over the first hour followed by 12.5 mg per hour over 4 hours (total dose 80 mg furoscix) using the pre-programmed on-body infusor with prefilled cartridge.

3 Studies Submitted

3.1 Studies Reviewed:

Subcutaneous infusion of furoscix in rabbits are reviewed.

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3.1 Previous Reviews Referenced:

The sponsor relies on the information under NDA 18667 to support the nonclinical safety of furosemide injection IV and IM at pH 8.3 to 9.0.

4 Pharmacology

4.1 Primary Pharmacology

Furosemide acts by inhibiting the renal Na^+-K^+-$2Cl^-$ co-transporter at the luminal surface of the thick ascending limb of the loop of Henle in the kidney, causing a profound diuresis.

4.2 Secondary Pharmacology

The diuretic effect of furosemide is associated with hypokalemia, metabolic alkalosis, hyperuricemia, and dehydration, leading to hypotension.

4.3 Safety Pharmacology

No safety pharmacology studies on subcutaneously administered furoscix have been conducted. The safety pharmacology is relied on the listed drug furosemide injection (IV, IM) in the NDA 18667.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

No nonclinical pharmacokinetic studies using subcutaneously administered furoscix have been conducted. The main difference between furoscix and the listed drug are the concentration of furosemide (8 mg/mL versus 10 mg/mL, respectively) and the inclusion of (b) (4) tromethamine hydrochloride (b) (4) (b) (4)

5.1.1 Absorption/Distribution

In tissue distribution studies in rats, intraperitoneally administered ^{14}C-furosemide distributed to six organs with highest tissue concentration in the adrenal > lung > kidney > spleen > pancreas > liver. Furosemide is 91-99% bound to plasma proteins, mainly to albumin, and the unbound fraction averages 2.3 to 4.1% at therapeutic concentrations. The terminal half-life of furosemide is approximately 2 hours.

5.1.2 Metabolism

In rats, metabolites were predominantly detected in the bile; whereas in the urine, the parent furosemide and some metabolites were detected. *In vitro* and *in vivo* studies using various CYP450 inducers and inhibitors showed that furosemide is metabolized by CYP2C11, 2E1, 3A1, and/or 3A2. Furosemide glucuronide is the major biotransformation product of furosemide.

5.1.3 Excretion

Furosemide is excreted in urine with 80 - 90% unchanged.

6 General Toxicology

6.1 Single-Dose Toxicity

Single dose subcutaneous infusion of furoscix in rabbit

Study #:	scF PC001 (5000487)
Study report location:	(b) (4)
Date of study completion:	December 5, 2014
GLP compliance:	GLP compliant
Drug:	Furoscix (buffered furosemide Tris HCl pH 7.4, 8 mg/ml) Phase I study:- Batch #: VL-016, Purity: >98% Phase II study:- Batch #: 006E14
Formulation/Vehicle:	(b) (4) % sodium chloride injection, USP
Route:	Subcutaneous infusion via a surgically implanted catheter over 5 hrs
Dosages:	Phase I = 5, 10, 20, 40, 60 mg/kg (Table 4 A) Phase II = 60 mg/kg (Table 4 B)
Species	New Zealand white rabbit
Age:	5.4 to 6.3 months old, Weight: 2.1 to 2.9 kg
Number of rabbits:	Phase I = 1/sex/dose, escalating 4 doses, 24 hr washout Phase II = 3/sex/dose, single MTD

Experimental design: In the Phase I study design, dose levels of 5, 10, 20, 40, and 60 mg/kg were administered, with a 24-hour observation period between escalating doses, and animals were euthanized on Day 3 (Table 4A). In Phase II study design, 60 mg/kg (MTD) was administered to further assess the local toxicity of furoscix injection solution at the site of subcutaneous infusion, and observed for 14 days (Table 4B).

Table 4A. Phase I experimental design (n=1 M, 1 F)

Group No.	Dose Level (mg/kg/day)	Infusion Rate (mL/kg/hr)[b]	Dose Concentration (mg/mL)
1/ (1st dose)[a]	5	0.237/0.099	7.9
2/ (2nd dose)[a]	10	0.475/0.198	7.9
3/ (3rd dose)[a]	20	0.949/0.396	7.9
4/ (4th dose)[a]	40	1.899/0.791	7.9
5/ (5th dose)[a]	60	2.848/1.187	7.9

Table 4B. Phase II experimental design (n=3 M, 3 F)

Group No.	Dose Level (mg/kg/day)	Infusion Rate (mL/kg/hr)	Dose Concentration (mg/mL)
6/Vehicle Control	0	2.813/1.172[c]	0
7/scFurosemide	60	2.813/1.172[c]	8.0

[a] Single administration followed by a 24-hour observation period between doses.
[b,c] Infusion rate during the first hour/infusion rate for the remaining 4 hours.

Surgical procedures: In anesthetized rabbits, small incision was made at the mid-lumbar site and a subcutaneous pocket was created with catheter inserted from the base of the neck to the lumbar region. The test-article was administered by subcutaneous infusion via the surgically implanted catheter for 5 hours on a single dose and escalating doses. Phase I groups received a single dose of furoscix followed by an observation period of 24 hours between escalating dosages, and thereafter, animals were euthanized on Day 3 (Table 4A). In Phase II, furoscix was administered for 5 hrs, and animals were observed for 14 days following dose administration (Table 4B).

Mortality: One male at 60 mg/kg was electively euthanized on Day 13 due to poor clinical condition related to severe scabbed, red cutaneous lesion at the infusion site. Macroscopically, the skin at the infusion site appeared dark, depressed and ulcerated, associated with marked necrotizing and ulcerative inflammation with bacteria in the epidermis/dermis, extending to the cutaneous muscle. The thickened and dark subcutis infusion site correlate microscopically to mixed cell inflammation with fibrinous material and wound, indicating infection at the inserted catheter.

Body weights/Food consumption: No furoscix injection related changes in bodyweight or food consumption were observed.

Clinical observations: Clear urine and/or clear liquid material was observed at 0 to 2 hours post-dose in the cage tray of all Phase II animals given 60 mg/kg, but not in the control group, indicating diuresis in the treatment group. There were no other clinical observations that occurred during this study related to the administration of furoscix.

Hematology: In Phase II animals, there were increases in red blood cell parameters (red blood cell count, hemoglobin, hematocrit; up to 1.18x, compared to control) on Day 2 in the 60 mg/kg dose group, and thereafter returned to the mean values of control group, indicating that the changes may be due to dehydration caused by furoscis. There were no furoscix-related changes in coagulation parameters compared to control group animals over the course of this study.

Clinical chemistry: In Phase II animals, moderate increases in urea nitrogen (up to 2.16x controls) with concurrent decreases in potassium (as low as 0.82x controls) and chloride (as low as 0.88x controls) were observed in the 60 mg/kg dose group on Day 2. Increases in creatine kinase were noted in males and females (7.17x and10.54x controls, respectively), which were reversed to values comparable to control group during the 14-day recovery period, indicating that the changes may be a consequence of diuresis caused by furoscix.

Local irritation assessment: In Phase 1 of the study, very slight erythema was observed post-dose in both animals given 5 mg/kg, in one male given 40 mg/kg, and in one male given 60 mg/kg. In Phase 2 of the study, two cases of infection at the infusion site (1 treatment group, 1 control group) were observed. One male in the Phase 2 treatment group was pre-terminally euthanized on Day 13 due to the presence of skin lesion with increasing severity at the infusion site. The cause of the lesion was determined to be bacterial skin infection, and a similar infection was observed in a Phase 2 vehicle control animal upon terminal euthanasia. At the end of the infusion, the surgically placed catheters were clipped and allowed to slip under the skin, resulting in infections in these two animals, indicating infusion site lesions related to study procedures.

Gross pathology: Macroscopic observations at the infusion site and subcutis were considered secondary to the experimental procedure. Other gross findings were considered incidental that are commonly observed in this strain and age of rabbit.

Organ weights: No test item-related organ weight changes were noted.

Histopathology: At the infusion site, mild necrotizing and focally ulcerative inflammation was noted at the epidermis/dermis of a single vehicle control animal. The necrotizing and ulcerative inflammation was similar to the cutaneous lesion noted in the preterminally euthanized furoscix-treated animal and was considered to be related to the experimental procedures. All other microscopic changes at the infusion site were of similar incidence and severity in vehicle control and furoscix-treated animals and were considered to be related to the experimental procedures.

Summary of findings: Administration of furoscix by a single 5-hour subcutaneous infusion was well-tolerated in male and female rabbits at dosage up to 60 mg/kg. Clinical pathology changes of dehydration and electrolyte imbalance were observed the day after administration of 60 mg/kg over 5 hours, indicating that pharmacologically active dose was reached. There were no furoscix-related changes in gross or microscopic changes related to the administration of the study drug. The local erythema at the infusion site were due to the

surgically placed catheters and study procedures. Thus, administration of furoscix by a single 5-hour subcutaneous infusion at up to 60 mg/kg (HED 19.5 mg/kg) was not associated with local toxicity.

6.2 Repeat-Dose Toxicity

No repeat-dose toxicity studies of subcutaneously administered furoscix have been conducted.

7 Genetic Toxicology

(adapted from labeling for furosemide injection, NDA 18667) https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=018667

Furosemide was non-mutagenic in various strains of Salmonella typhimurium when tested in the presence or absence of an *in vitro* metabolic activation system, and questionably positive for gene mutation in mouse lymphoma cells in the presence of rat liver S9 at the highest dose tested. Furosemide did not induce excess sister chromatid exchange in human cells *in vitro*, but other studies on chromosomal aberrations in human cells *in vitro* gave conflicting results. In Chinese hamster cells, furosemide induced chromosomal damage but was questionably positive for excess sister chromatid exchange. Studies on the induction by furosemide of chromosomal aberrations in mice were inconclusive, but the urine of rats treated with furosemide did not induce gene conversion in Saccharomyces cerevisiae.

8 Carcinogenicity

(adapted from labeling for furosemide injection, NDA 18667) https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=018667

Furosemide was tested for carcinogenicity by oral administration in one strain of mice and one strain of rats, which showed a small but significantly increased incidence of mammary gland carcinomas in female mice at a dosage (b) (4) (b) (4) times that at the maximum human dose of 80 mg (b) (4) There were marginal increases in uncommon tumors in male rats at a dose of 15 mg/kg (b) (4) (b) (4) but not at 30 mg/kg (b) (4) (b) (4) (b) (4).

9 Reproductive and Developmental Toxicology

(adapted from labeling for furosemide injection, NDA 18667) https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=018667

9.1 Fertility and Developmental Toxicology

Furosemide did not impair fertility in male or female rats, at 100 mg/kg/day (b) (4) (b) (4) (the maximum effective diuretic dose in the rat and (b) (4) times that at the maximal human dose of 80 mg (b) (4)).

9.2 Embryonic Fetal Developmental

Furosemide caused unexplained maternal deaths and abortions in the rabbit at the lowest dose of 25 mg/kg (b) (4) (b) (4). In another study, a dose of 50 mg/kg (b) (4) (b) (4) also caused maternal deaths and abortions when administered to rabbits between Days 12 and 17 of gestation. In a third study, none of the pregnant rabbits survived an oral dose of 100 mg/kg (b) (4) (b) (4). Data from the above studies indicate fetal lethality that can precede maternal deaths. The results of the mouse study and one of the three rabbit studies also showed an

increased incidence and severity of hydronephrosis (distention of the renal pelvis and the ureters) in fetuses derived from the treated dams as compared with the incidence of fetuses from the control group (b) (4).

10 Special Toxicology Studies

10.1 Local Tolerance

Local tolerance study of furoscix in rabbits is described in the General Toxicology Section 6.

10.2 Juvenile toxicity

In juvenile male rats ages 4, 6, or 10 weeks, administration of furosemide 40 mg/kg intraperitoneally as a single dose per day for 2 weeks caused nephrocalcinosis. Kidney calcification was observed as early as three days following treatment, with maximum calcification at day 5, indicating that nephrocalcinosis develops within a few days of furosemide administration.

11 Integrated Summary and Safety Evaluation

Administration of furoscix (buffered furosemide) as a single 5-hour subcutaneous infusion via a surgically implanted catheter in the New Zealand White rabbit was well-tolerated at dosages up to 60 mg/kg and observed for 14 days. The animals showed diuresis, indicating efficacy of subcutaneously administered furoscix. There were slight increases in red blood cell parameters (red blood cell count, hemoglobin, hematocrit), creatine kinase and urea nitrogen, and decrease in potassium and chloride, all of which returned to the mean control values during recovery period, indicating that the changes may be due to dehydration and electrolytes imbalance. There were no furoscix-related changes in coagulation parameters compared to control group animals over the course of the study. Positive macroscopic findings at the infusion site and subcutis were considered secondary to the experimental procedure and not related to the test item. Microscopic changes at the infusion site were of similar incidence and severity in the vehicle control group and furoscix-treated animals, and were also considered procedure rather than drug related effects. A transient erythema was noted at 1-hour post end of infusion, but not beyond 1-hour post-dose, indicating experimental procedure effect. Edema noted at 60 mg/kg dose level may be due to the increased volume administered to achieve the targeted dose. There was no evidence of local irritation at the infusion site. Thus, administration of furoscix by a single 5-hour subcutaneous infusion at 60 mg/kg (HED 19.5 mg/kg) was not associated with any local toxicity. The infusion dosage is about 15-fold higher than human dosage of 80 mg furosemide (1.33 mg/kg) injected IV or IM.

12 Labeling

Updated labeling of furosemide based on new label format.

(b) (4)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application NDA number:	209988, [505(b)2]
Supporting document/s:	Original e-submission, eCTD sequence # 0000
CDER stamp date:	8/23/2017
Review completion date:	4/30/2018
Product:	Furosemide subcutaneous delivery (Furoscix Infusor Drug-device combination product)
Indication:	Treatment of edema associated with congestive heart failure
Applicant:	scPharmaceuticals, Inc., Lexington, MA
Review Division:	Cardiovascular and Renal Drug Products (DCRP/ODE1/OND/CDER)
Reviewer:	Belay Tesfamariam, PhD
Team Leader:	Jean Wu, PhD
Division Director:	Norman Stockbridge, MD, PhD
Project Manager:	Brian Proctor

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TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

In patients with increased signs and symptoms of heart failure, intravenous furosemide is administered in an outpatient clinic in a special infusion centers known as 'diuresis clinics', in the emergency room, or during an in-patient stay. In order to reduce the burden of heart failure management, the sponsor proposes that subcutaneously administered furosemide could be easier to prepare and administer, while maintaining similar diuretic efficacy as intravenous administration. The sponsor has developed a pH neutral, buffered furosemide formulation (furoscix), optimized for subcutaneous delivery via a wearable Infusor device applied onto the abdomen. The Infusor consists of a reusable activator controller containing ancillary electronics, and a disposable single-use cartridge, a micro-piston pump, an automatic needle insertion and retraction, and an adhesive backing that holds the system onto the user's skin. In this 505(b)(2) NDA application, the nonclinical information on furosemide is relied on the previously approved drug products to support this application for the treatment of edema associated with congestive heart failure. In this NDA, the sponsor's data on subcutaneously administered to-be-marketed formulation of furoscix in rabbits are reviewed.

1.2 Brief Discussion of Nonclinical Findings

The nonclinical studies examined local tolerability of subcutaneously infused furoscix, buffered furosemide pH 7.4, via surgically implanted catheter at the base of the neck to the caudal part of the lumbar in New Zealand White rabbits. Administration of a single 5-hour subcutaneous infusion of furoscix was well-tolerated in male and female rabbits at dosages up to 60 mg/kg/day and a 14-day observation period. The animals dosed at 60 mg/kg showed increased urine output indicating diuresis efficacy of subcutaneously administered furosemide. There were slight increases in red blood cell parameters (red blood cell count, hemoglobin, hematocrit), creatine kinase and urea nitrogen, and decrease in serum potassium and chloride. All values returned to the control levels during recovery period, indicating that the changes may be secondary to dehydration and electrolytes imbalance following diuresis. There were no furoscix-related changes in coagulation parameters compared to control group animals. There was no gross or microscopic evidence of local irritation at the infusion site. In the drug product, a degradation product (b) (4) was identified, and it is qualified using toxicology studies in rats and rabbits. Leachables and extractables form the infusor device were below the threshold for toxicological concern. In addition, qualification of total extractables from the components of the Infusor device was made using the International Standard for biological evaluation of medical devices. Based on this study, subcutaneous infusion of furoscix at a dose level of 60 mg/kg (720 mg/m^2, HED 19.5 mg/kg) in the rabbit is approximately 15-fold higher than human dosage of furosemide 80 mg (49 mg/m^2, 1.33 mg/kg) injection.

(HED = human equivalent dose).

1.3 Recommendations

1.3.1 Approvability

Furoscix administered subcutaneously is considered to be sufficiently tolerable. Nonclinical studies were not performed on the performance of the wearable infusor device, and hence the approvability of the drug-device combination product to efficiently deliver furoscix will rely on its performance in humans.

1.3.2 NonClinical Comments

Furosemide injection at a pH of 8.3 - 9.0 is associated with stinging and discomfort during injection, and thus formulation of a neutral pH of 7.4 may reduce or ease pH-related discomfort at injection site. The preclinical studies using a subcutaneously administered buffered furosemide did not reveal any irritation or other local reaction, however, local discomfort or irritation following administration of the study drug using a wearable Infusor cannot be excluded.

1.3.3 Labeling

Furosemide labeling is updated on carcinogenesis, reproductive and developmental toxicology (see Page 15).

2 Drug Information

2.1 Drug

CAS registry number: 54-31-9

International nonproprietary name: Furosemide

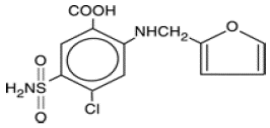
Buffered furosemide formulation: Furoscix

Chemical name: 4-chloro-N-furfuryl-5-sulfamoylanthranilic acid;
5-(aminosulfonyl)-4-chloro-2[(2-furanylmethyl)-amino]-benzoic acid

Chemical formula: $C_{12}H_{11}ClN_2O_5S$

Molecular weight: 330.75 daltons

Structure formula:



Pharmacologic class: Loop diuretic

Route of administration: Subcutaneous

Drug delivery system: Furoscix Infusor

2.2 Relevant INDs, NDAs, and DMFs

NDA 18667 - Reference listed drug (furosemide injection, IV and IM, pH 8.3 to 9.0).

2.3 Drug Formulation

Furoscix is buffered furosemide with tromethamine hydrochloride (Tris HCl) to a pH of 7.4 (7.0 - 7.8) to improve tolerability during subcutaneous administration (Table 1). Furoscix is to be administered via a wearable Infusor that delivers 80 mg of furosemide subcutaneously over 5 hours.

Table 1: Composition of drug product

Ingredients	Composition		Function
	Quantity	Percent	
Active Substances(s)			
Furosemide	8 mg/mL	~0.8	Active ingredient
Excipients			
Tris HCl	7.88 mg/mL	~0.8	(b) (4)
Sodium Chloride	5.84 mg/mL	~0.6	
Hydrochloric Acid	qs to pH 7.4	-	pH adjustment
Sodium Hydroxide	qs to pH 7.4	-	pH adjustment
Water for Injection	qs to 1 mL	-	(b) (4)

2.4 Comments on Novel Excipients

There are no novel excipients. Inactive ingredients in the formulation include sodium chloride and tromethamine (Tris HCl), which are used as an excipient in approved solutions for injection and topical formulations.

2.5 Comments on Impurities/Degradants

In the drug product, (b) (4) was identified as a degradation product ((b) (4) ppm). Qualification of (b) (4) impurity at a level of (b) (4) % was based on a wide margin of safety using toxicology studies that include a 6-day subcutaneous toxicity study with a (b) (4) structural analog in the rabbit, a 13-week oral (diet) toxicity study with (b) (4) in the rat, and a 28-day dermal toxicity study with (b) (4) in the rat (Table 2). In addition, studies in transgenic mice showed that (b) (4) is not genotoxic *in vivo*. Studies in the rat and rabbit also showed that (b) (4) is not a teratogen.

Table 2: Calculated safety margins for (b) (4) at an impurity level of (b) (4)

Endpoint	Study/Species	Route	NOAEL (mg/kg/day)	Safety Margin*	Adjusted Safety Margin**
Systemic (Liver)	6-day rabbit study w/ (b) (4)	S.C.	(b) (4)		
Systemic (Liver)	13-week rat study (b) (4)	Oral			
Local (Dermal application site)	28-day rat study (b) (4)	Dermal			
(b) (4)					

2.6 Leachables and extractables

Extractable studies performed by GC-MS identified several organic chemicals in the sc2Wear patch pump cartridge, but none were (b) (4) µg/device, which is below the threshold of toxicological concern (1.5 µg/day/lifetime, ICH M7). For the 8 leachable elements in the infusor device, none was at the level of toxicological concern. In the furosemide injection drug product, three non-volatile leachables, including (b) (4) (b) (4) were identified in the glass vial and stopper. The levels of the leachables were qualified using ICH Q3B qualification threshold of 0.5% or 200 µg total daily intake.

Further qualification of total extractables from the components of the Infusor device, that include the vial, vial adapter, and cartridge [redacted] (b) (4) were made using biocompatibility study report submitted to the CDRH as part of the device testing. The tests include cytotoxicity (mouse fibroblast cells), sensitization (guinea pig maximization), irritation (intracutaneous in rabbits), primary skin irritation (shaved skin rabbit), systemic toxicity (IV, IP mice), hemocompatibility (hemolysis assay), and pyrogenicity (febrile response in rabbits) (Table 3). The results of the total extractables provide additional evidence in support of the ICH M7 qualification for impurities. Whether the device meets the biocompatibility requirements of the International Standard ISO 10993 for biological evaluation of medical devices is under review by the CDRH.

Table 3: GLP biocompatibility studies of the Infusor device (Reviewed under PMA P140032)

Study/ Guideline	Summary
Cytotoxicity ISO 10993-5 Report-0046 Report-0039 Report-0040	**Infusor Components** • The Cartridge and Vial Adapter component test samples with a Grade 0 showed no evidence of causing any cell lysis or toxicity. **Skin-Contacting Components** • No cytotoxic effect was observed.
Sensitization ISO 10993-10 Report-0037 Report 0113	**Fluid Contacting Surfaces** • No sensitization responses (eg, erythema and edema) were observed. **Skin Contacting Surfaces** • No sensitization responses were observed.
Irritation or Intracutaneous Reactivity ISO 10993-10 Report-0116 Report-0038	**Intracutaneous Irritation** • No signs of irritation were identified. **Skin Irritation** • No signs of irritation were observed.
Acute Systemic Toxicity ISO 10993-11 Report 0109	• No evidence of acute systemic toxicity was identified.
Material-Mediated Pyrogenicity USP Pyrogen Test Procedure, Section <151> USP38 Report-0112	• None of the rabbits (n=3) administered the test article extract had a temperature rise ≥0.5 °C at the required observation points. These results indicate that the test article was non-pyrogenic.
Subacute/Subchronic Toxicity ISO 10993-11 Report-0030 Report-0031	**Subacute** • No toxicities related to the test article were observed. **Subchronic** • No toxicities related to the test article were observed.
Hemocompatibility	• Components tested were determined to be non-hemolytic.
ASTM Guideline (F756-13) Report-0114	
Implantation ISO 10993-6 Report-0122	• No abnormal clinical signs were identified and there were no adverse gross and histopathology findings. The test article was considered a non-irritant.

2.7 Proposed Clinical Population and Dosing Regimen

Furosemide for subcutaneous infusion is indicated for the treatment of edema associated with congestive heart failure at a dosage of 80 mg over 5 hours, administered as 30 mg over the first hour followed by 12.5 mg per hour over 4 hours (total 50 mg). Pharmacokinetic clinical study to bridge the buffered furoscix and the currently approved IV administration of furosemide, injection solution, using a commercially available external infusion system for subcutaneous administration showed comparable diuresis with subcutaneous furosemide when compared to the same dose administered intravenously.

2.8 Regulatory Background

Furosemide has a long history of use for the treatment of edema associated with congestive heart failure (CHF), renal disease, and cirrhosis. Furosemide has been approved in the US since 1966 as an oral tablet form and later approved in 1968 as an injection formulation for IV and IM administration and as an oral solution. There are no furosemide products for subcutaneous administration approved by the FDA.

Infusor delivery device

Nonclinical studies were not performed on the performance of the wearable infusor device.

3 Studies Submitted

3.1 Studies Reviewed:

In this NDA, the sponsor's data on subcutaneously administered to-be-marketed formulation of furoscix in rabbits are reviewed.

3.1 Previous Reviews Referenced:

The sponsor relies on the information under NDA 18667 to support the nonclinical safety of furosemide injection IV and IM at pH 8.3 to 9.0.

4 Pharmacology

4.1 Primary Pharmacology

Furosemide acts by inhibiting the renal Na^+-K^+-$2Cl^-$ co-transporter at the luminal surface of the thick ascending limb of the loop of Henle in the kidney, causing a profound diuresis. In general, IV administration exhibits the quickest onset of diuresis, and subcutaneous administration take longer to reach peak effect. Constant rate IV infusion exhibited better diuretic efficacy compared to an IV bolus administration, suggesting that higher C_{max} is not associated with greater diuretic effects. Thus, furoscix administered by subcutaneous infusion would exhibit consistent diuresis than a subcutaneous bolus administration.

4.2 Secondary Pharmacology

The diuretic effect of furosemide can cause hypokalemia, metabolic alkalosis, hyperuricemia, and dehydration leading to hypotension.

4.3 Safety Pharmacology

The safety pharmacology is relying on the listed drug furosemide injection (IV, IM) in the NDA 18667. No safety pharmacology studies on subcutaneously administered furoscix have been conducted by the Sponsor.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Relevant nonclinical literature covering the pharmacokinetics of furosemide was obtained from public scientific databases. No nonclinical pharmacokinetic studies using subcutaneously administered furoscix have been conducted by the Sponsor. The main differences between furoscix and the listed drug are the concentration of furosemide (8 mg/mL versus 10 mg/mL, respectively) and the inclusion of [redacted] (b) (4) tromethamine hydrochloride [redacted] (b) (4)). These differences are not expected to alter the pharmacokinetics of furosemide.

5.1.1. Absorption/Distribution

In tissue distribution studies in rats, ^{14}C-furosemide administered intraperitoneally distributed in the order of adrenal>lung>kidney>spleen>pancreas>liver for the six organs with the highest tissue/plasma concentration ratios. Furosemide is 91 - 99% bound to plasma proteins, mainly to albumin. The unbound fraction averages 2.3 to 4.1% at therapeutic concentrations. The terminal half-life of furosemide is approximately 2 hours.

5.1.2. Metabolism

Furosemide glucuronide is the major biotransformation product of furosemide in man.

5.1.3. Excretion

Furosemide is excreted in urine unchanged 80 - 90%. Furosemide clearance is decreased and the half-life was increased in reduced renal function.

5.2 Toxicokinetics

The absorption of furoscix after subcutaneous administration is expected to be slower with a reduced C_{max} compared to IV furosemide injection. This was confirmed in the clinical pharmacokinetic study (scP-01-002) comparing furoscix administered subcutaneously to the LD administered intravenously. The C_{max} value for the IV administration was 4.2 times higher than that from the subcutaneous administration; however, the total extent of furosemide systemic exposure (AUC) from the subcutaneous administration was similar to the IV treatment arm and both routes of administration produced similar diuresis.

6 General Toxicology

The general toxicology is relying on the listed drug furosemide injection (IV, IM) in the NDA 18667. The nonclinical safety of the buffered furosemide administered subcutaneously in the rabbit is reviewed in this NDA.

6.1 Single-Dose Toxicity

Single dose subcutaneous infusion of furoscix in rabbit

Study no.:	scF_PC001 (5000487)
Study report location:	(b) (4)
Date of study completion:	December 5, 2014
GLP compliance:	Yes
Drug:	Furoscix (buffered furosemide Tris HCl pH 7.4, 8 mg/ml) Phase I study:- Batch #: VL-016, Phase II study:- Batch #: 006E14
Formulation/Vehicle:	(b) (4) % sodium chloride injection, USP
Route:	Subcutaneous infusion via a surgically implanted catheter over 5 hrs
Dosages:	Phase I = 5, 10, 20, 40, 60 mg/kg/day (Table 4) Phase II = 60 mg/kg/day
Species	New Zealand white rabbit
Age:	5.4 to 6.3 months old, Weight: 2.1 to 2.9 kg
Number of rats:	Phase I = 1/sex/dose, escalating 4 doses, 24 hr washout Phase II = 3/sex/dose, single MTD

Experimental design: In the Phase I study design, dose levels of 5, 10, 20, 40, and 60 mg/kg/day were administered, with a minimum 24-hour observation period between escalating doses, and animals were euthanized on Day 3 (Table 4A). In Phase II study design, the MTD (60 mg/kg) was administered to further assess the local toxicity of furoscix injection solution at the site of subcutaneous infusion, and observed for 14 days (Table 4B).

Table 4A. Phase I experimental design (n=1M, 1 F)

Group No.	Dose Level (mg/kg/day)	Infusion Rate (mL/kg/hr)[b]	Dose Concentration (mg/mL)
1/ (1st dose)[a]	5	0.237/0.099	7.9
2/ (2nd dose)[a]	10	0.475/0.198	7.9
3/ (3rd dose)[a]	20	0.949/0.396	7.9
4/ (4th dose)[a]	40	1.899/0.791	7.9
5/ (5th dose)[a]	60	2.848/1.187	7.9

Table 4B. Phase II design (n= 3M, 3 F)

Group No.	Dose Level (mg/kg/day)	Infusion Rate (mL/kg/hr)	Dose Concentration (mg/mL)
6/Vehicle Control	0	2.813/1.172[c]	0
7/scFurosemide	60	2.813/1.172[c]	8.0

[a] Single administration followed by a 24-hour observation period between doses.
[b,c] Infusion rate during the first hour/infusion rate for the remaining 4 hours.

Surgical procedures: In anesthetized rabbits, small incision was made at the mid-lumbar site and a subcutaneous pocket was created with catheter inserted from the base of the neck to the lumbar region. The test-article was administered by subcutaneous infusion via the surgically implanted catheter for 5 hours on a single dose and escalating doses. Phase I groups received a single dose of furosemide followed by an observation period of 24 hours between escalating dosages, and thereafter animals were euthanized on Day 3 (Table 4A). In Phase II, furosemide was administered for 5 hrs, and animals were observed for 14 days following dose administration (Table 4B).

Mortality: One male at 60 mg/kg/day was electively euthanized on Day 13 due to a poor clinical condition related to severe scabbed, red cutaneous lesion at the infusion site. Macroscopically, the skin at the infusion site appeared dark, depressed and ulcerated, associated with marked necrotizing and ulcerative inflammation with bacteria of the epidermis/dermis, extending to the cutaneous muscle. Additional macroscopic observations at the infusion site of a thickened and dark subcutis correlated microscopically to mixed cell inflammation in the subcutis, with fibrinous material, hemorrhage and bacteria, extending to

vessels with thrombosis, suggesting an infection at the site of the catheter which was left in situ.

Body weights/Food consumption: There were no furoscix injection solution related changes in bodyweight or food consumption.

Clinical observations: Clear urine and/or clear liquid material was observed 0 to 2 hours post-dose in the cage tray of all Phase II animals given 60 mg/kg/day, but not in the control group, indicating diuresis in the treatment group. There were no other clinical observations that occurred during this study related to the administration of furosemide.

Hematology: In Phase II animals, there were increases in red blood cell parameters (red blood cell count, hemoglobin, hematocrit; up to 1.18x, mean compared to control group mean) in males and females given 60 mg/kg/day on Day 2, which returned to the mean values of control group, indicating that the changes may be due to dehydration caused by furosemide. There were no furoscix-related changes in coagulation parameters compared to control group animals over the course of this study.

Clinical chemistry: In Phase II animals, moderate increases in urea nitrogen (up to 2.16x controls) with concurrent decreases in potassium (as low as 0.82x controls) and chloride (as low as 0.88x controls) were observed in the 60 mg/kg/day dose group on Day 2. Increases in creatine kinase were noted in males and females (7.17x and10.54x controls, respectively), which were reversed to values comparable to control group during the 14-day recovery period, indicating that the changes may be a consequence of diuresis caused by furoscix.

Local irritation assessment: During Phase 1 of the study, very slight erythema was observed post-dose in both animals given 5 mg/kg, in one male given 40 mg/kg, and in one male given 60 mg/kg. One female exhibited well-defined erythema 1-hour after the end of the infusion that was resolved by the 2-hour (post-end of infusion) observation time point. In Phase 2 of the study, two cases of infection at the infusion site (1 treatment group, 1 control group) were observed. One male in the Phase 2 treatment group was pre-terminally euthanized on Day 13 due to the presence of a skin lesion of increasing severity at the infusion site. The cause of the lesion was determined to be a bacterial skin infection; a similar infection was observed in a Phase 2 vehicle control animal upon terminal euthanasia. Therefore, these infusion site lesions were determined to be related to study procedures; specifically, at the end of the infusion, the surgically placed catheters were clipped and allowed to slip under the skin, resulting in the infections in these two animals.

Gross pathology: Macroscopic observations at the infusion site and subcutis were considered secondary to the experimental procedure and not related to the test article. All other gross findings observed were considered incidental, of the nature commonly observed in this strain and age of rabbit, and/or were of similar incidence in control and treated animals.

Organ weights: No test item-related organ weight changes were noted.

Histopathology: At the infusion site, mild necrotizing and focally ulcerative inflammation was noted at the epidermis/dermis of a single vehicle control animal. The necrotizing and ulcerative inflammation was similar to the cutaneous lesion noted in the

preterminally euthanized furoscix-treated animal and was considered to be related to the experimental procedures. All other microscopic changes at the infusion site were of similar incidence and severity in vehicle control and furoscix-treated animals and were also considered to be related to the experimental procedures, and not an effect of the test article.

Key study findings: Administration of furoscix by a single 5-hour subcutaneous infusion was well-tolerated in male and female rabbits at dosage up to 60 mg/kg/day. Clinical pathology changes consistent with dehydration and electrolytes imbalance were observed the day after 60 mg/kg dosage administration, indicating that the maximum tolerated systemic dose was reached. There were no furoscix-related effects on local irritation assessment at the infusion site, nor were there any gross or microscopic changes related to the administration of the study drug. Dehydration and electrolyte imbalance were observed the day after administration of 60 mg/kg over 5 hours, indicating that pharmacologically active dose was reached. Thus, administration of furoscix by a single 5-hour subcutaneous infusion at up to 60 mg/kg (720 mg/m^2, HED 19.5 mg/kg) was not associated with any local toxicity. This dosage is about 15-fold higher than that at the approved human dose of furosemide 80 mg (49 mg/m^2, 1.33 mg/kg) injected intramuscularly or intravenously.
(HED = human equivalent dose)

6.2 Repeat-Dose Toxicity

No repeat-dose toxicity studies of subcutaneously administered furoscix have been conducted by the Sponsor.

7 Genetic Toxicology

The following information regarding genotoxicity is obtained from the approved labeling of furosemide.

Furosemide was non-mutagenic in various strains of Salmonella typhimurium when tested in the presence or absence of an *in vitro* metabolic activation system, and questionably positive for gene mutation in mouse lymphoma cells in the presence of rat liver S9 at the highest dose tested. Furosemide did not induce excess sister chromatid exchange in human cells *in vitro*, but other studies on chromosomal aberrations in human cells *in vitro* gave conflicting results. In Chinese hamster cells, furosemide induced chromosomal damage but was questionably positive for excess sister chromatid exchange. Studies on the induction by furosemide of chromosomal aberrations in mice were inconclusive, but the urine of rats treated with furosemide did not induce gene conversion in Saccharomyces cerevisiae.

8 Carcinogenicity

The following information regarding carcinogenicity is taken from the approved labeling of furosemide injection.

Furosemide was tested for carcinogenicity by oral administration in one strain of mice and one strain of rats, which showed a small but significantly increased incidence of mammary gland carcinomas in female mice at a dosage (b) (4) times (b) (4) the (b) (4) human dose of 80 mg (b) (4) There were marginal increases in

uncommon tumors in male rats at a dose of 15 mg/kg [redacted] but not at 30 mg/kg ([redacted]

Literature search on carcinogenicity of furosemide:

In a carcinogenicity study of furosemide, rats and mice (n=50/sex/group) were exposed daily to furosemide for two years through their diets at 350, or 700 ppm (estimated 15 and 30 mg/kg/day) and 700, or 1400 ppm (estimated 95 and 200 mg/kg/day), respectively (Bucher et al., 1990). Male rats exhibited increased severity of nephropathy compared to controls, and parathyroid hyperplasia was increased in high-dose male rats. Adenomas and adenocarcinomas were observed only in male rats, but there was no statistically significant difference in incidence rates between control and treatment groups. Meningiomas were observed in 3/50 low-dose male rats and were considered to be the cause of death in these rats; the incidence rate was not statistically different from control. In female rats, there was a marginal increase in the incidence of C-cell adenomas, and one case of C-cell carcinoma was observed in a low-dose female rat.

In mice, the survival of the high-dose group of females was significantly lower than that of controls after week 99 (18/50 compared to 36/50, respectively) (Bucher et al., 1990). Adenocarcinomas of the mammary gland occurred only in dosed female mice, and the incidence in the high-dose group was increased compared to controls. No adenocarcinomas metastasized to other organs. The incidences and severity of nephropathy were increased in treated male and female mice over two years, and one tubular cell adenoma was observed in a high-dose male mouse. Mice treated with furosemide also exhibited increased hematopoiesis; the increase was hypothesized to be due to increased demand for leukocytes as a result of increased inflammation in the urogenital tract and elsewhere.

9 Reproductive and Developmental Toxicology

Summary of reproductive and developmental toxicity from approved label of furosemide injection and published articles.

9.1 Fertility and Developmental Toxicology

Furosemide did not impair fertility in male or female rats, at 100 mg/kg/day [redacted] (the maximum effective diuretic dose in the rat and [redacted] times that at the maximal human dose of 80 mg [redacted]).

9.2 Embryonic Fetal Developmental

Furosemide caused unexplained maternal deaths and abortions in the rabbit at the lowest dose of 25 mg/kg ([redacted]. In another study, a dose of 50 mg/kg [redacted] also caused maternal deaths and abortions when administered to rabbits between Days 12 and 17 of gestation. In a third study, none of the pregnant rabbits survived an oral dose of 100 mg/kg [redacted]. Data from the above studies indicate fetal lethality that can precede maternal deaths. The results of the mouse study and one of the three rabbit studies also showed an increased incidence and severity of hydronephrosis (distention of the renal pelvis and the ureters) in fetuses derived from the treated dams as compared with the

incidence of fetuses from the control group, (b) (4) (b) (4) .

Literature search on reproductive toxicology of furosemide

In near-term pregnant rats (gestational day 21), subcutaneous injection of furosemide (1, 10, and 100 mg/kg) 4 hours before delivery caused significant delays in postnatal ductus arteriosus closure for up to 60 minutes after birth at all dose levels compared to controls (Toyoshima et al., 2010).

In neonatal rats, injection of furosemide 1 or 10 mg/kg within 3 minutes of birth, induced significant delay in the closure of ductus arteriosus compared to control group (Toyoshima et al., 2010). At 120 min after birth, the mean ductus arteriosus diameter in the 10 mg/kg group (0.14 mm) remained significantly greater than that of the control and 1 mg/kg groups (0.02 mm and 0.02 mm, respectively). If furosemide has similar effects in human preterm neonates, caution may be warranted in its use in the treatment of infants with patent ductus arteriosus. In another study in neonatal rats, Injection of furosemide (1 mg/kg) induced ductus arteriosus reopening was significantly inhibited by co-injection with indomethacin (10 mg/kg), indicating involvement of prostaglandins in the delay of postnatal ductus arteriosus closure (60 min after birth) (Toyoshima et al., 2010).

In another study in weaning male rats which received enalapril (2.5 mg/d), furosemide (40 mg/d), or both drugs in food for 6 weeks, enalapril was associated with lower body weights, and furosemide was associated with increased 24-hr urine output (Lane, 1995). Systolic blood pressure was not significantly altered by any of the treatment regimens. Kidney weights and volume were increased in the furosemide treatment groups compared to control and enalapril groups. The gross structures of the kidneys were not noticeably different between treatment groups, though furosemide increased plasma renin activity, cortical tubular growth, glomerular volume, and filtration surface area per glomerulus. Concurrent administration of enalapril blocked the furosemide-induced changes to filtration surface area and glomerular growth.

10 Special Toxicology Studies

10.1 Local Tolerance

Local tolerance study of furoscix in rabbits is described in the General Toxicology Section 6. Overall, subcutaneous infusion of furoscix was well-tolerated at dosages up to 60 mg/kg, which was also determined to be a pharmacologically active dose based on the dehydrating effects noted.

10.2 Juvenile toxicity

In juvenile male rats ages 4, 6, or 10 weeks, administration of furosemide 40 mg/kg intraperitoneally as a single dose per day for 2 weeks caused nephrocalcinosis of similar magnitudes (Osorio et al., 1998). Kidney calcification was observed as early as three days into treatment in the 4- and 10-week-old rats, with maximum calcification at day 5. Rats treated with furosemide gained less weight and had higher urine output and fluid intake than

age-matched controls. These observations indicate that nephrocalcinosis develops within a few days of furosemide administration in an age-independent manner induced by the loop diuretic itself.

11 Integrated Summary and Safety Evaluation

Furosemide has been safely administered for more than 40 years for the treatment of edema associated with CHF, cirrhosis of the liver and renal disease. The clinical safety of furosemide is well-established, with known risks associated with excessive diuresis. The major findings from the nonclinical information evaluated included dehydration, electrolyte imbalance, and nephrosis. In developmental and juvenile toxicity studies, furosemide treatment led to abnormal ductus arteriosus closure and kidney calcification. Furosemide induced chromosomal aberrations in *in vitro* studies, but was otherwise not found to be mutagenic or genotoxic. In carcinogenicity studies, marginal increases in mammary gland carcinomas were observed in female mice and marginal increases in uncommon tumors were observed in male rats.

The sponsor has developed a buffered injection solution of furoscix at a level of 8 mg/ml and pH 7.4 for subcutaneous administration. The nonclinical studies were aimed to examine local tolerability of subcutaneously infused furoscix via a surgically implanted catheter in New Zealand White rabbits. Administration of furoscix as a single 5-hour subcutaneous infusion was well-tolerated at dosages up to 60 mg/kg/day, and observed for 14 days. The animals dosed at 60 mg/kg showed diuresis, indicating efficacy of subcutaneously administered furosemide. In the 60 mg/kg dose group, there were slight increases in red blood cell parameters (red blood cell count, hemoglobin, hematocrit), creatine kinase and urea nitrogen, and decrease in potassium and chloride, all of which returned to the mean control values during recovery period, indicating that the changes may be due to dehydration and electrolytes imbalance. There were no furoscix-related changes in coagulation parameters compared to control group animals over the course of this study.

Positive macroscopic findings at the infusion site and subcutis were considered secondary to the experimental procedure and not related to the test item. Microscopic changes at the infusion site were of similar incidence and severity in the vehicle control group and furoscix-treated animals, and were also considered procedure rather than drug related effects. A transient erythema was noted at the 1-hour post end of infusion, but no erythema was observed beyond 1-hour post-dose, and this finding was considered to be experimental procedure effect. The edema noted at 60 mg/kg/day dose level may be attributed to the increased volume administered to achieve the required dosage. There was no evidence of local irritation assessment at the infusion site. Thus, administration of furoscix by a single 5-hour subcutaneous infusion at 60 mg/kg (720 mg/m^2, HED 19.5 mg/kg) was not associated with any local toxicity. The infusion dosage is about 15-fold higher than that at the approved human dosage of 80 mg furosemide (49 mg/m^2, 1.33 mg/kg) injected IV or IM.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Furoscix administered subcutaneously is considered to be sufficiently tolerable. The approvability of the wearable Infusor device to efficiently deliver furoscix will rely on its performance in humans.

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(b) (4)

12 References

Bucher JR, Huff J, Haseman JK, Eustis SL, Davis WE JR, Meierhenry EF. Toxicology and carcinogenicity studies of diuretics in F344 rats and B6C3F1 mice. 2. Furosemide. Journal of Applied Toxicology. 1990;10(5):369-378.

Hospira (2016). Approved labeling for furosemide injection, USP. NDA 18667. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=018667

Lane PH. Furosemide treatment, angiotensin II, and renal growth and development in the rat. Pediatric Research. 1995;37:747-754.

Osorio AV, Alon MM, Nichols MA, Alon US. Effect of age on furosemide-induced nephrocalcinosis in the rat. Biology of the neonate. 1998;73:306-312.

Toyoshima K, Momma K, Nakanishi T. In vivo dilatation of the ductus arteriosus induced by furosemide in the rat. Pediatric Research. 2010;67:173-176.

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