HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SOFDRA™ safely and effectively. See full prescribing information for SOFDRA.

SOFDRA (sofpironium) topical gel, 12.45%
Initial U.S. Approval: 2024

INDICATIONS AND USAGE

SOFDRA is an anticholinergic indicated for the treatment of primary axillary hyperhidrosis in adults and pediatric patients 9 years of age and older (1).

DOSAGE AND ADMINISTRATION

Apply 1 pump of SOFDRA per underarm once a day at bedtime. For topical use only (2).

DOSAGE FORMS AND STRENGTHS

Topical gel: 12.45% of sofpironium (3).

CONTRAINDICATIONS

Medical conditions that can be exacerbated by the anticholinergic effect of SOFDRA (e.g., glaucoma, paralytic ileus, unstable cardiovascular status in acute hemorrhage, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis, myasthenia gravis, Sjögren's syndrome) (4).

WARNINGS AND PRECAUTIONS

- Urinary Retention: Use with caution in patients with a history or presence of documented urinary retention. Discontinue use immediately and consult a healthcare provider should any signs or symptoms of urinary retention develop (5.1).
- Control of Body Temperature: Watch for generalized lack of sweating when in hot or very warm environmental temperatures and avoid using SOFDRA if not sweating under these conditions (5.2).
- Operating Machinery or an Automobile: Transient blurred vision may occur with use of SOFDRA. If blurred vision occurs, discontinue use and avoid operating a motor vehicle or other machinery until symptoms resolve (5.3).

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥2%) are dry mouth, vision blurred, application site pain, application site erythema, mydriasis, application site dermatitis, application site pruritus, urinary retention, and application site irritation (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Botanix SB Inc. at 1-866-763-6337 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Anticholinergics: Coadministration of SOFDRA with anticholinergic medications may result in additive interaction leading to an increase in anticholinergic adverse effects. Avoid coadministration of SOFDRA with other anticholinergic-containing drugs (7.1).
- Strong Inhibitors of CYP2D6: Avoid co-administration of SOFDRA with drugs that are strong inhibitors of CYP2D6 (7.2).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 07/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SOFDRA is indicated for the treatment of primary axillary hyperhidrosis in adults and pediatric patients 9 years of age and older.

2 DOSAGE AND ADMINISTRATION

- Do not shave armpits at least 8 hours before applying SOFDRA.
- Do not shower at least 30 minutes before applying SOFDRA.
- Apply SOFDRA to clean, dry skin once a day at bedtime.
- Apply a single pump actuation to the top of the supplied applicator. Spread the entire amount to cover 1 underarm. Apply a separate, single pump actuation to the top of the supplied applicator. Apply the entire amount to the second underarm. Allow to dry completely (5 minutes) before putting on clothing.
- Wash hands immediately with soap.
- For topical use only.
- Avoid fire, flame, and smoking during and immediately following application.
- Do not shower or wash underarms for at least 8 hours after application.
- Do not touch underarms after applying SOFDRA.
- Do not use more than once daily.
- Avoid transfer of SOFDRA to the periocular area *[see Warnings and Precautions (5.3)]*.
- Do not apply SOFDRA to broken skin.
- Avoid using SOFDRA with occlusive dressings.

3 DOSAGE FORMS AND STRENGTHS

Topical gel: 12.45% (w/w) of sofpironium in a 50 mL bottle with a metered dose pump and applicator. One full pump delivers 72 mg sofpironium in 0.67 mL of gel.

4 CONTRAINDICATIONS

SOFDRA is contraindicated in patients with medical conditions that can be exacerbated by the anticholinergic effect of sofpironium bromide (e.g., glaucoma, paralytic ileus, unstable cardiovascular status in acute hemorrhage, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis, myasthenia gravis, Sjögren's syndrome).

5 WARNINGS AND PRECAUTIONS

5.1 Urinary Retention

Use SOFDRA with caution in patients with a history or presence of documented urinary retention. Prescribers and patients should be alert for signs and symptoms of urinary

retention (e.g., difficulty passing urine, distended bladder), especially in patients with prostatic hypertrophy or bladder-neck obstruction. Discontinue use immediately and consult a healthcare provider should any of these signs or symptoms develop.

5.2 Control of Body Temperature

In the presence of high ambient temperature, heat illness (hyperpyrexia and heat stroke due to decreased sweating) can occur with the use of anticholinergic drugs, including SOFDRA. Watch for generalized lack of sweating when in hot or very warm environmental temperatures and avoid using SOFDRA if not sweating under these conditions.

5.3 Operating Machinery or an Automobile

Transient blurred vision may occur with use of SOFDRA. If blurred vision occurs, discontinue use and avoid engaging in activities that require clear vision, such as operating a motor vehicle or other machinery or performing hazardous work, until the symptoms have resolved.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

Urinary Retention *[See Warnings and Precautions (5.1)].*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In two double-blind, vehicle controlled clinical trials (CARDIGAN 1 and CARDIGAN 2) of 700 subjects 10 to 76 years of age (353 subjects treated with SOFDRA and 347 subjects treated with vehicle), 44% of subjects were male, 79% were White, 21% were Black, and 1% were Asian. A total of 618 subjects completed at least 6 weeks of treatment, including 307 subjects treated with SOFDRA and 311 subjects treated with vehicle.

Table 1 summarizes the most frequent adverse reactions (≥2%) in subjects with primary axillary hyperhidrosis treated with SOFDRA.

Table 1: Adverse Reactions Occurring in ≥2% of Subjects with Primary Axillary Hyperhidrosis Treated with SOFDRA in Trials CARDIGAN 1 and 2

Adverse Reactions	SOFDRA (N = 353) n (%)	Vehicle (N = 347) n (%)
Dry mouth	51 (14%)	2 (0.6%)
Vision blurred	30 (9%)	1 (0.3%)
Mydriasis	23 (7%)	0
Urinary retention	8 (2%)	0

Note: COVID-19 was observed in 8 (2%) SOFDRA and 2 (0.6%) vehicle subjects.

Table 2 shows the local skin reactions reported ≥2%, which occurred more commonly in the SOFDRA group.

Table 2: Local Skin Reactions Reported in ≥2% of Subjects with Primary Axillary Hyperhidrosis Treated with SOFDRA in Trials CARDIGAN 1 and 2

Local Skin Adverse Reactions	SOFDRA (N = 353) n (%)	Vehicle (N = 347) n (%)
Pain	29 (8%)	6 (2%)
Erythema	23 (7%)	1 (0.3%)
Dermatitis	21 (6%)	1 (0.3%)
Pruritus	16 (5%)	2 (0.6%)
Irritation	8 (2%)	1 (0.3%)
Exfoliation	7 (2%)	1 (0.3%)

In an open-label, long-term safety trial (ARGYLE), 197 subjects were treated for 48 weeks with SOFDRA. Adverse reactions occurring at a frequency ≥2% were vision blurred (19%), dry mouth (17%), application site pruritus (15%), application site pain (15%), application site dermatitis (11%), application site erythema (8%), application site irritation (6%), mydriasis (5%), application site rash (4%), upper respiratory tract infection (4%), dry eye (4%), urinary retention (4%), application site exfoliation (3%), application site folliculitis (3%), hypertension (3%), application site dryness (2%), viral upper respiratory tract infection (2%), influenza (2%), and headache (2%).

7 DRUG INTERACTIONS

7.1 Anticholinergics

Coadministration of SOFDRA with anticholinergic medications may result in additive interaction leading to an increase in anticholinergic adverse effects *[See Warnings and Precautions (5.2)* and *Adverse Reactions (6.1)]*. Avoid coadministration of SOFDRA with other anticholinergic-containing drugs.

7.2 Strong Inhibitors of CYP2D6

Avoid co-administration of SOFDRA with drugs that are strong inhibitors of CYP2D6.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data with SOFDRA use in pregnant women to evaluate for drug-associated risks of major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies, subcutaneous administration of sofpironium bromide to pregnant rats and rabbits during the period of organogenesis resulted in no significant adverse effects at doses 31 and 10 times, respectively, the maximum recommended human dose (MRHD) (*see Data*).

The background risks of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defects, loss, and other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In an embryofetal development study in rats, sofpironium bromide was not associated with embryofetal lethality or fetal malformations at subcutaneous dose levels of 1, 3, and 10 mg/kg/day administered during the period of organogenesis. The maternal and fetal survival, growth and development no observed adverse effect level (NOAEL) was 10 mg/kg/day (31 times the MRHD based on AUC comparisons).

In an embryofetal development study in rabbits, sofpironium bromide was administered by subcutaneous injection to pregnant rabbits at doses of 0.4, 2 and 10 mg/kg/day during the period of organogenesis. Maternal toxicity as evidenced by decreased maternal body weight gain and feed consumption was observed in all sofpironium bromide treated groups. The decrease in maternal body weight was considered severe at 10 mg/kg/day and was associated with embryofetal lethality. The maternal toxicity NOAEL could not be established in the study. The NOAEL for embryo-fetal development toxicity was 2 mg/kg/day (10 times the MRHD based on AUC comparison). Fetal malformation was not observed with sofpironium bromide treatment at doses up to 10 mg/kg/day (57 times the MRHD based on AUC comparison) in rabbits.

In a pre- and postnatal development study, sofpironium bromide was administered by subcutaneous injection to pregnant rats at doses of 1, 3 and 6 mg/kg/day beginning on gestation day 6 through lactation day 20. Maternal toxicity associated with a 17% decrease in body weight gain noted at 6 mg/kg/day (approximately 19 times the MRHD based on AUC comparisons) when compared to the control group. No sofpironium bromide-related effects on prenatal and postnatal development, neurobehavioral or reproductive performance of offspring were noted at doses up to 6 mg/kg/day (approximately 19 times the MRHD based on AUC comparison).

8.2 Lactation

Risk Summary

There are no data on the presence of SOFDRA or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for SOFDRA and any potential adverse effects on the breastfed infant from sofpironium bromide or from the underlying maternal condition.

Sofpironium bromide was detected in milk following single subcutaneous administration to lactating rats (*see Data*). When a drug is present in animal milk, it is likely that the drug will be present in human milk.

Data

Animal Data

Milk excretion studies in vivo showed sofpironium or its metabolites were transferred into the milk after a single subcutaneous administration of 0.5 mg/kg to lactating rats on postnatal day 10.

8.4 Pediatric Use

The safety, effectiveness, and pharmacokinetics of SOFDRA for the treatment of primary axillary hyperhidrosis have been established in pediatric patients 9 years of age and older *[See Clinical Pharmacology (12.3)]*. Use of SOFDRA in this age group is supported by evidence from two multicenter, randomized, double-blind, parallel-group, vehicle-controlled 6-week trials and two multicenter, open-label, 24-week and 48-week trials, which included 72 pediatric subjects 9 years of age and older *[See Adverse Reactions (6.1) and Clinical Studies (14)]*.

The safety and effectiveness of SOFDRA have not been established in pediatric patients younger than 9 years of age.

8.5 Geriatric Use

Clinical trials of SOFDRA did not include sufficient numbers of subjects aged 65 years and older to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

8.6 Renal Impairment

The safety and effectiveness of SOFDRA in populations with renal impairment have not been established.

8.7 Hepatic Impairment

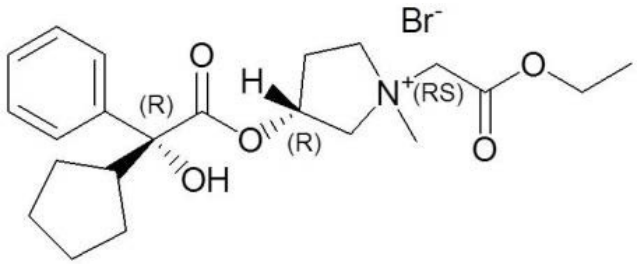
The safety and effectiveness of SOFDRA in populations with hepatic impairment have not been established.

10 OVERDOSAGE

In case of an overdose, remove the topically applied product with soap and water, and treat the symptoms and signs attributed to the overdose symptomatically. Consider contacting the Poison Center at 1-800-222-1222 for the latest recommendations.

11 DESCRIPTION

SOFDRA (sofpironium) topical gel is an anticholinergic drug. Sofpironium bromide drug substance is a white to off white powder with the chemical name 3'(R)-[2(R) cyclopentylphenylhydroxy-acetoxy]-1'-methyl-1'-ethoxycarbonylmethyl-pyrrolidinium bromide, very soluble in chloroform and freely soluble in water, ethanol, acetonitrile, and methanol, molecular formula of $C_{22}H_{32}BrNO_5$, molecular weight of 470.4 g/mol, and the following structural formula:



SOFDRA is a clear to translucent, colorless to pale yellow viscous gel containing 12.45% (w/w) sofpironium (equivalent to 15% sofpironium bromide) in an airless bottle sealed with a multi-dose metered pump. Each pump delivers 72 mg of sofpironium (equivalent to 87 mg of sofpironium bromide) in 0.67 mL of gel. The inactive ingredients are citric acid, 77.2% v/v dehydrated alcohol, hexylene glycol, hydroxypropyl cellulose, and isopropyl myristate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sofpironium bromide is a competitive inhibitor of acetylcholine receptors that are located on certain peripheral tissues, including sweat glands. Sofpironium bromide indirectly reduces the rate of sweating by preventing the stimulation of these receptors.

12.2 Pharmacodynamics

Pharmacodynamics of SOFDRA are unknown.

Cardiac Electrophysiology

At an exposure 3 times the exposure associated with the maximum approved recommended dose, SOFDRA does not prolong the QTc interval to any clinically relevant extent.

12.3 Pharmacokinetics

Absorption

The pharmacokinetics of sofpironium were evaluated in adult patients with primary axillary hyperhidrosis following SOFDRA applied once daily to the underarms for 21 days. The mean ± standard deviation (SD) exposures of sofpironium in adults are presented in Table 3. There was no evidence of accumulation.

Table 3: Mean (SD) Plasma Exposure of Sofpironium in Adults with Primary Axillary Hyperhidrosis Following SOFDRA Application on Day 1

PK Parameter	Adult Patients
C_{max} (ng/mL)	2.71 (6.94)
AUC_{0-t} (ng·hr/mL)	45.1 (85.1)
t_{max} (hr)	5.34 (5.45)

Distribution

Plasma protein binding of sofpironium is around 34.8-37.8%. The major sofpironium metabolite (BBI-4010) had plasma protein binding around 2.3-3.7%.

Elimination

Metabolism

Sofpironium is metabolized by nonenzymatic hydrolysis, CYP2D6 and CYP3A4 mediated-oxidative metabolism, and glycine conjugation. In plasma, sofpironium was the major component (38%) followed by the BBI-4010 (20%) metabolite.

Excretion

Urinary excretion of sofpironium and BBI-4010 were less than 0.5% of the applied dose.

Specific Populations

The pharmacokinetics of sofpironium were not evaluated in pregnant patients or patients with hepatic or renal impairment.

Pediatric Subjects

The mean ± SD exposures of sofpironium after a single dose in pediatric subjects 9 years to 16 years of age are presented in Table 4. After 24 weeks of dosing, trough concentrations of sofpironium were low and there was no evidence of accumulation. The exposure to major metabolite (BBI-4010) in pediatric subjects was similar to sofpironium exposure in adults.

Table 4: Mean (SD) Plasma Exposure of Sofpironium in Pediatric Subjects Following Single Dose Administration of SOFDRA on Day 1

PK Parameter	Pediatric Patients
C_{max} (ng/mL)	1.30 (3.16)
AUC_{0-t} (ng·hr/mL)	14.6 (35.0)
t_{max} (hr)	4.0 (0.9, 23.1)

t_{max} reported as median and range.

Drug Interaction Studies

No clinically significant differences in sofpironium pharmacokinetics were observed when used concomitantly with inhibitors of CYP3A4, OCT2, MATE1, or MATE2-K.

In vivo Study

In presence of 20 mg oral dose of paroxetine HCl (strong CYP2D6 inhibitor) C_{max} and AUC_{0-t} of sofpironium increased by approximately twofold compared to when SOFDRA was administered alone.

In vitro Studies

Sofpironium is an inhibitor of CYP2D6, CYP3A4, OCT1, OCT2, and MATE1 in vitro. Sofpironium is not an inducer of CYP1A2, CYP2B6, or CYP3A4.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of sofpironium bromide was assessed in a 2-year dermal mouse carcinogenicity study and a 2-year subcutaneous rat carcinogenicity study. There were no drug-related neoplasms associated with daily topical administration of sofpironium bromide topical gel to mice at doses of up to 20% sofpironium bromide (2 times and 11 times the MRHD based on AUC comparisons for males and females, respectively). No drug-related neoplasms were identified in rats administered daily subcutaneous doses up to 1.5 mg/kg/day (males) and 5.0 mg/kg/day (females) (4 times and 12 times the MRHD based on AUC comparisons for males and females, respectively).

Sofpironium bromide was not mutagenic in a bacterial mutagenicity assay (Ames assay) or clastogenic in an in vitro mammalian chromosomal aberration assay (human peripheral blood lymphocytes) or in an in vivo micronucleus assay in rats.

There were no sofpironium bromide-related effects on male or female fertility and early embryonic developmental endpoints in rats at subcutaneous doses up to 10 mg/kg/day (70 and 20 times the MRHD based on AUC comparisons for males and females, respectively).

14 CLINICAL STUDIES

Two randomized, vehicle-controlled multicenter trials, CARDIGAN 1 (NCT03836287) and CARDIGAN 2 (NCT03948646), enrolled a total of 701 subjects 10 years of age or older with primary axillary hyperhidrosis. All subjects were to have symptoms of axillary hyperhidrosis for at least 6 months' duration, produce at least 50 mg of sweat in each axilla (underarm) with a combined total of at least 150 mg over a 5-minute period, and have a Hyperhidrosis Disease Severity Measure-Axillary, 7-item scale score (HDSM-Ax-7) ≥3.

In the trials, 56% of subjects were female, 78% were White, and 20% were Black or African American; for ethnicity, 31% identified as Hispanic or Latino. Fewer than 1% of subjects were less than 12 years of age, 7% were 12 to 17 years of age, 91% were 18 to 64 years of age, and 1% were 65 years of age or older.

Subjects 12 years of age and older were asked to rate their underarm sweating severity and frequency since waking on the previous day ("since you woke up yesterday") on the 11-item HDSM-Ax Adult version instrument. The HDSM-Ax-7 scale score was calculated by taking an average of 7 items, where the scale score ranges from 0 to 4 with a higher score representing greater underarm sweating severity. The mean HDSM-Ax-7 scale score at Baseline was 3.5 in CARDIGAN 1, and 3.6 in CARDIGAN 2. The median gravimetric sweat production (GSP) over 5 minutes at Baseline was 214.1 mg in the SOFDRA arm and 228.6 mg in the vehicle arm in CARDIGAN 1, and 207.7 mg in the SOFDRA arm and 231.1 mg in the vehicle arm in CARDIGAN 2.

Subjects were randomized to receive either SOFDRA or vehicle applied once daily at bedtime to each axilla. The co-primary endpoints were the proportion of subjects having at least a 2-point improvement in the HDSM-Ax-7 scale score from Baseline to Day 43, and the change in GSP from Baseline to Day 43.

The results of CARDIGAN 1 and CARDIGAN 2 are presented in Table 5.

Table 5: Primary Efficacy Endpoints at Day 43 in Subjects with Primary Axillary Hyperhidrosis in Trials CARDIGAN 1 and 2

	CARDIGAN 1		CARDIGAN 2	
	SOFDRA	**Vehicle**	**SOFDRA**	**Vehicle**
≥2 point Improvement in HDSM-Ax-7[a] scale score from Baseline to Day 43 in subjects 12 years of age and older	N = 172 49%	N= 177 29%	N = 178 64%	N = 169 48%
Treatment Difference 95% Confidence Interval	18% (8%, 29%)		17% (6%, 27%)	
Baseline Median GSP[b] in subjects 10 years of age and older (mg/5 minutes)	N = 173 214	N = 177 229	N = 180 208	N = 171 231
Change from Baseline to Day 43 Median (mg/5 minutes) 25th percentile, 75th percentile	-128 -201, -52	-100 -228, -29	-143 -260, -75	-134 -230, -60

[a] Hyperhidrosis Disease Severity Measure-Axillary, 7-item score
[b] Gravimetric Sweat Production

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

SOFDRA topical gel is supplied in a bottle with a multi-dose metered pump, applicator, and cap. Each bottle contains 50 mL of gel with a multi-dose pump capable of dispensing 60 pump actuations. Each pump actuation dispenses 0.67 mL of gel.

NDC 83723-010-50

Storage and Handling

Store upright at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

SOFDRA is flammable; keep away from heat or flame.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Urinary Retention

Instruct patients to be alert for signs and symptoms of urinary retention (e.g., difficulty passing urine, distended bladder). Instruct patients to discontinue use and consult a healthcare provider immediately should any of these signs or symptoms develop *[see Warnings and Precautions (5.1)]*.

Control of Body Temperature

Advise patients that in the presence of high ambient temperature, heat illness due to decreased sweating can occur with the use of SOFDRA. Advise patients to watch for generalized lack of sweating when in hot or very warm environmental temperatures and to avoid using SOFDRA if not sweating under these conditions *[see Warnings and Precautions (5.2)]*.

Operating Machinery or an Automobile

Advise patients that transient blurred vision may occur with SOFDRA. If this occurs, instruct patients to contact their healthcare provider, discontinue use of SOFDRA, and avoid operating a motor vehicle or other machinery or performing hazardous work until symptoms resolve *[see Warnings and Precautions (5.3)]*.

Instructions for Administering SOFDRA

Advise patients as follows *[see Dosage and Administration (2)]*:

- Do not shave armpits at least 8 hours before applying SOFDRA.
- Do not shower at least 30 minutes before applying SOFDRA.
- Apply 1 pump actuation per underarm to clean, dry skin once a day at bedtime (total 2 pumps). Allow to dry completely (5 minutes) before putting on clothing.
- Wait at least 8 hours after applying the gel to shower or wash underarms.
- Do not use SOFDRA more frequently than once daily.
- Instruct patients to wash their hands with soap and water immediately after applying SOFDRA.
- Instruct patients not to apply SOFDRA to other body areas or to broken skin and to avoid using SOFDRA with occlusive dressings.
- SOFDRA is flammable; avoid fire, flame, and smoking during and immediately following application.

Manufactured for:

Botanix SB Inc.
Phoenix, AZ 85016