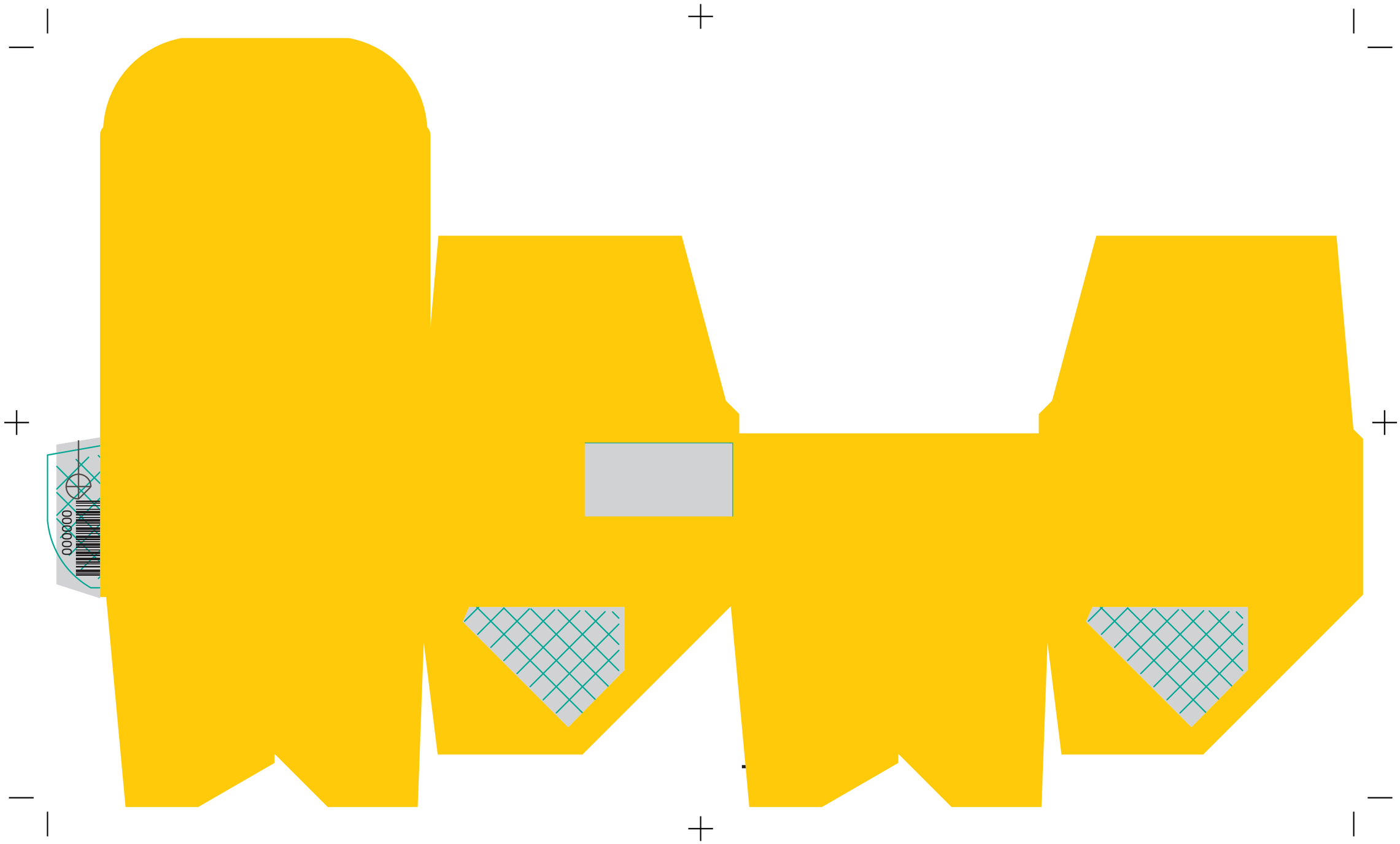

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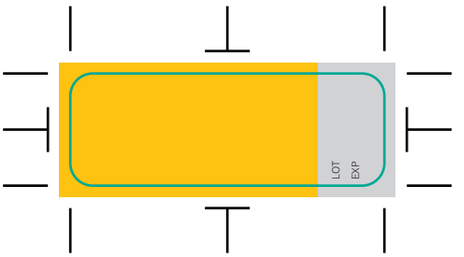

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Vasostrict™
(vasopressin injection, USP)
For Intravenous Infusion

3003373

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

Vasostrict (vasopressin injection) for intravenous use
Initial U.S. Approval: 2014

----------INDICATIONS AND USAGE----------
- Vasostrict is indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines. (1)

----------DOSAGE AND ADMINISTRATION----------
- Dilute Vasostrict with normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W) to either 0.1 units/mL or 1 unit/mL for intravenous administration. Discard unused diluted solution after 18 hours at room temperature or 24 hours under refrigeration. (2.1)
- Post-cardiotomy shock: 0.03 to 0.1 units/minute (2.2)
- Septic shock: 0.01 to 0.07 units/minute (2.2)

----------DOSAGE FORMS AND STRENGTHS ----------
- Injection: 20 units per mL; packaged as 1 mL per vial (3)

----------CONTRAINDICATIONS----------
- Vasostrict is contraindicated in patients with known allergy or hypersensitivity to 8-L-arginine vasopressin or chlorobutanol. (4)

----------WARNINGS AND PRECAUTIONS----------
- Can worsen cardiac function. (5.1)

----------ADVERSE REACTIONS----------
The most common adverse reactions include decreased cardiac output, bradycardia, tachyarrhythmias, hyponatremia and ischemia (coronary, mesenteric, skin, digital). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical, Inc. at 1-800-828-9393 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------
- Pressor effects of catecholamines and Vasostrict are expected to be additive. (7.1)
- Indomethacin may prolong effects of Vasostrict. (7.2)
- Co-administration of ganglionic blockers or drugs causing SIADH may increase the pressor response. (7.3, 7.5)
- Co-administration of drugs causing diabetes insipidus may decrease the pressor response. (7.6)

----------USE IN SPECIFIC POPULATIONS----------
- **Pregnancy:** May induce uterine contractions. (8.1)
- **Pediatric Use:** Safety and effectiveness have not been established. (8.4)
- **Geriatric Use:** No safety issues have been identified in older patients. (8.5)

Revised: 5/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Vasostrict™ is indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation of Diluted Solutions

Dilute Vasostrict in normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W) prior to use. Discard unused diluted solution after 18 hours at room temperature or 24 hours under refrigeration.

Table 1 Preparation of diluted solutions

Fluid restriction?	Final concentration	Mix	
		Vasostrict	Diluent
No	0.1 units/mL	2.5 mL (50 units)	500 mL
Yes	1 unit/mL	5 mL (100 units)	100 mL

Inspect parenteral drug products for particulate matter and discoloration prior to use, whenever solution and container permit.

2.2 Administration

The goal of treatment is optimization of perfusion to critical organs, but aggressive treatment can compromise perfusion of organs, like the gastrointestinal tract, whose function is difficult to monitor. The following advice is empirical. In general, titrate to the lowest dose compatible with a clinically acceptable response.

For post-cardiotomy shock, start with a dose of 0.03 units/minute. For septic shock, start with a dose of 0.01 units/minute. If the target blood pressure response is not achieved, titrate up by 0.005 units/minute at 10- to 15-minute intervals. The maximum dose for post-cardiotomy shock is 0.1 units/minute and for septic shock 0.07 units/minute. After target blood pressure has been maintained for 8 hours without the use of catecholamines, taper Vasostrict by 0.005 units/minute every hour as tolerated to maintain target blood pressure.

3 DOSAGE FORMS AND STRENGTHS

Injection: 20 units per mL; packaged as 1 mL per vial

4 CONTRAINDICATIONS

Vasostrict is contraindicated in patients with known allergy or hypersensitivity to 8-L-arginine vasopressin or chlorobutanol.

5 WARNINGS AND PRECAUTIONS

5.1 Worsening Cardiac Function

Use in patients with impaired cardiac response may worsen cardiac output.

6 ADVERSE REACTIONS

The following adverse reactions associated with the use of vasopressin were identified in the literature. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to estimate their frequency reliably or to establish a causal relationship to drug exposure.

Bleeding/lymphatic system disorders: Hemorrhagic shock, decreased platelets, intractable bleeding

Cardiac disorders: Right heart failure, atrial fibrillation, bradycardia, myocardial ischemia

Gastrointestinal disorders: Mesenteric ischemia

Hepatobiliary: Increased bilirubin levels

Renal/urinary disorders: Acute renal insufficiency

Vascular disorders: Distal limb ischemia

Metabolic: Hyponatremia

Skin: Ischemic lesions

7 DRUG INTERACTIONS

7.1 Catecholamines

Use with *catecholamines* is expected to result in an additive effect on mean arterial blood pressure and other hemodynamic parameters.

7.2 Indomethacin

Use with *indomethacin* may prolong the effect of Vasostrict on cardiac index and systemic vascular resistance *[see Clinical Pharmacology (12.3)]*.

7.3 Ganglionic Blocking Agents

Use with *ganglionic blocking agents* may increase the effect of Vasostrict on mean arterial blood pressure *[see Clinical Pharmacology (12.3)]*.

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7.4 Furosemide

Use with *furosemide* increases the effect of Vasostrict on osmolar clearance and urine flow *[see Clinical Pharmacology (12.3)].*

7.5 Drugs Suspected of Causing SIADH

Use with *drugs suspected of causing SIADH* (e.g., SSRIs, tricyclic antidepressants, haloperidol, chlorpropamide, enalapril, methyldopa, pentamidine, vincristine, cyclophosphamide, ifosfamide, felbamate) may increase the pressor effect in addition to the antidiuretic effect of Vasostrict.

7.6 Drugs Suspected of Causing Diabetes Insipidus

Use with *drugs suspected of causing diabetes insipidus* (e.g., demeclocycline, lithium, foscarnet, clozapine) may decrease the pressor effect in addition to the antidiuretic effect of Vasostrict.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary: There are no adequate or well-controlled studies of Vasostrict in pregnant women. It is not known whether vasopressin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Animal reproduction studies have not been conducted with vasopressin *[see Clinical Pharmacology (12.3)].*

Clinical Considerations: Because of increased clearance of vasopressin in the second and third trimester, the dose of Vasostrict may need to be up-titrated to doses exceeding 0.1 units/minute in post-cardiotomy shock and 0.07 units/minute in septic shock.

Vasostrict may produce tonic uterine contractions that could threaten the continuation of pregnancy.

8.3 Nursing Mothers

It is not known whether vasopressin is present in human milk. However, oral absorption by a nursing infant is unlikely because vasopressin is rapidly destroyed in the gastrointestinal tract. Consider advising a lactating woman to pump and discard breast milk for 1.5 hours after receiving vasopressin to minimize potential exposure to the breastfed infant.

8.4 Pediatric Use

Safety and effectiveness of Vasostrict in pediatric patients with vasodilatory shock have not been established.

8.5 Geriatric Use

Clinical studies of vasopressin did not include sufficient numbers of subjects aged 65 and over 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 *[see Warnings and Precautions (5), Adverse Reactions (6), and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

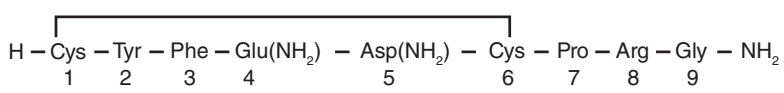
Overdosage with Vasostrict can be expected to manifest as consequences of vasoconstriction of various vascular beds (peripheral, mesenteric, and coronary) and as hyponatremia. In addition, overdosage may lead less commonly to ventricular tachyarrhythmias (including Torsade de Pointes), rhabdomyolysis, and non-specific gastrointestinal symptoms.

Direct effects will resolve within minutes of withdrawal of treatment.

11 DESCRIPTION

Vasopressin is a polypeptide hormone that causes contraction of vascular and other smooth muscles and antidiuresis. Vasostrict is a sterile, aqueous solution of synthetic arginine vasopressin for intravenous administration. The 1 mL solution contains vasopressin 20 units/mL, chlorobutanol, NF 0.5% as a preservative, and Water for Injection, USP adjusted with acetic acid to pH 3.4 – 3.6.

The chemical name of vasopressin is Cyclo (1-6) L-Cysteinyl-L-Tyrosyl-L-Phenylalanyl-L-Glutaminyl-L-Asparaginyl-L-Cysteinyl-L-Prolyl-L-Arginyl-L-Glycinamide. It is a white to off-white amorphous powder, freely soluble in water. The structural formula is:



Molecular Formula: $C_{46}H_{65}N_{15}O_{12}S_2$ Molecular Weight: 1084.23

One mg is equivalent to 530 units.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The vasoconstrictive effects of vasopressin are mediated by vascular V_1 receptors. Vascular V_1 receptors are directly coupled to phopholipase C, resulting in release of calcium, leading to vasoconstriction. In addition, vasopressin stimulates antidiuresis via stimulation of V_2 receptors which are coupled to adenyl cyclase.

12.2 Pharmacodynamics

At therapeutic doses exogenous vasopressin elicits a vasoconstrictive effect in most vascular beds including the splanchnic, renal and cutaneous circulation. In addition, vasopressin at pressor doses triggers contractions of smooth muscles in the gastrointestinal tract mediated by muscular V_1-receptors and release of prolactin and ACTH via V_3 receptors. At lower concentrations typical for the antidiuretic hormone vasopressin inhibits water diuresis via renal V_2 receptors.

In patients with vasodilatory shock vasopressin in therapeutic doses increases systemic vascular resistance and mean arterial blood pressure and reduces the dose requirements for norepinephrine. Vasopressin tends to decrease heart rate and cardiac output. The pressor effect is proportional to the infusion rate of exogenous vasopressin. Onset of the pressor effect of vasopressin is rapid, and the peak effect occurs within 15 minutes. After stopping the infusion the pressor effect fades within 20 minutes. There is no evidence for tachyphylaxis or tolerance to the pressor effect of vasopressin in patients.

12.3 Pharmacokinetics

At infusion rates used in vasodilatory shock (0.01-0.1 units/minute) the clearance of vasopressin is 9 to 25 mL/min/kg in patients with vasodilatory shock. The apparent $t_{1/2}$ of vasopressin at these levels is ≤10 minutes. Vasopressin is predominantly metabolized and only about 6% of the dose is excreted unchanged in urine. Animal experiments suggest that the metabolism of vasopressin is primarily by liver and kidney. Serine protease, carboxipeptidase and disulfide oxido-reductase cleave vasopressin at sites relevant for the pharmacological activity of the hormone. Thus, the generated metabolites are not expected to retain important pharmacological activity.

Drug-Drug Interactions

Indomethacin more than doubles the time to offset for vasopressin's effect on peripheral vascular resistance and cardiac output in healthy subjects *[see Drug Interactions (7.2)].*

The ganglionic blocking agent tetra-ethylammonium increases the pressor effect of vasopressin by 20% in healthy subjects *[see Drug Interactions (7.3)].*

Furosemide increases osmolar clearance 4-fold and urine flow 9-fold when co-administered with exogenous vasopressin in healthy subjects *[see Drug Interactions (7.4)].*

Halothane, morphine, fentanyl, alfentanyl and sufentanyl do not impact exposure to endogenous vasopressin.

Special Populations

Pregnancy: Because of a spillover into blood of placental vasopressinase the clearance of exogenous and endogenous vasopressin increases gradually over the course of a pregnancy. During the first trimester of pregnancy the clearance is only slightly increased. However, by the third trimester the clearance of vasopressin is increased about 4-fold and at term up to 5-fold. After delivery the clearance of vasopressin returns to pre-conception baseline within two weeks.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No formal carcinogenicity or fertility studies with vasopressin have been conducted in animals. Vasopressin was found to be negative in the *in vitro* bacterial mutagenicity (Ames) test and the *in vitro* Chinese hamster ovary (CHO) cell chromosome aberration test. In mice, vasopressin has been reported to have an effect on function and fertilizing ability of spermatozoa.

14 CLINICAL STUDIES

Increases in systolic and mean blood pressure following administration of vasopressin were observed in 7 studies in septic shock and 8 in post-cardiotomy vasodilatory shock.

16 HOW SUPPLIED/STORAGE AND HANDLING

Vasostrict (vasopressin injection, USP) is supplied in vials as follows:

A carton of 25 multi-dose vials each containing vasopressin 1 mL at 20 units/mL.

Store between 2°C and 8°C (36°F and 46°F). Do not freeze.

Discard vial after 48 hours after first puncture.

NDC 42023-164-25 (carton)

Manufactured by:
Par Pharmaceutical Companies, Inc.
Spring Valley, NY 10977

I05/14 OS164J-01-90-01

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