TIOPRONIN- tiopronin tablet, delayed release
Torrent Pharmaceuticals Limited

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TIOPRONIN DELAYED-RELEASE TABLETS safely and effectively. See full prescribing information for TIOPRONIN DELAYED-RELEASE TABLETS.

TIOPRONIN delayed-release tablets, for oral use
Initial U.S. Approval: 1988

INDICATIONS AND USAGE

Tiopronin delayed-release tablets are a reducing and complexing thiol indicated, in combination with high fluid intake, alkali, and diet modification, for the prevention of cystine stone formation in adults and pediatric patients 9 years of age and older with severe homozygous cystinuria, who are not responsive to these measures alone. (1)

DOSAGE AND ADMINISTRATION

- The recommended initial dosage in adult patients is 800 mg/day. In clinical studies, the average dosage was about 1,000 mg/day. (2.1)
- The recommended initial dosage in pediatric patients 9 years of age and older is 15 mg/kg/day. Avoid dosages greater than 50 mg/kg per day in pediatric patients. (5.1, 8.4)
- Measure urinary cystine 1 month after initiation of tiopronin delayed-release tablets and every 3 months thereafter (2.3)
- Administer tiopronin delayed-release tablets in 3 divided doses at the same times each day, without food. (2.1)

DOSAGE FORMS AND STRENGTHS

Tablets: 100 mg and 300 mg (3)

CONTRAINDICATIONS

- Hypersensitivity to tiopronin or any component of tiopronin delayed-release tablets (4)

WARNINGS AND PRECAUTIONS

- Proteinuria, including nephrotic syndrome, and membranous nephropathy, has been reported with tiopronin use. Pediatric patients receiving greater than 50 mg/kg of tiopronin per day may be at increased risk for proteinuria. (2.1, 5.1, 8.4)
- Hypersensitivity reactions have been reported during tiopronin treatment. (4, 5.2)

ADVERSE REACTIONS

Most common adverse reactions (≥10%) are nausea, diarrhea or soft stools, oral ulcers, rash, fatigue, fever, arthralgia, proteinuria, and emesis. (6)
To report SUSPECTED ADVERSE REACTIONS, contact Torrent Pharma Inc. at 1-800-912-9561 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Lactation: Breastfeeding is not recommended. (8.2)
- Geriatric: Choose dose carefully and monitor renal function in the elderly. (8.5)

Additional pediatric use information is approved for Mission Pharmacal Company's Thiola EC (tiopronin delayed-release) tablets. However, due to Mission Pharmacal Company's marketing exclusivity rights, this drug product is not labeled with that information.
See 17 for PATIENT COUNSELING INFORMATION.

Revised: 2/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Tiopronin delayed-release tablets are indicated, in combination with high fluid intake, alkali, and diet modification, for the prevention of cystine stone formation in adults and pediatric patients 9 years of age and older with severe homozygous cystinuria, who are not responsive to these measures alone.

Additional pediatric use information is approved for Mission Pharmacal Company's Thiola EC (tiopronin delayed-release) tablets. However, due to Mission Pharmacal Company's marketing exclusivity rights, this drug product is not labeled with that information.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Adults: The recommended initial dosage in adult patients is 800 mg/day. In clinical studies, the average dosage was about 1,000 mg/day.

Pediatrics: The recommended initial dosage in pediatric patients 9 years of age and older is 15 mg/kg/day. Avoid dosages greater than 50 mg/kg per day in pediatric patients *[see Warnings and Precautions (5.1), Use in Specific Populations (8.4)]*.

Administer tiopronin delayed-release tablets in 3 divided doses at the same times each day, without food.

Consider starting tiopronin delayed-release tablets at a lower dosage in patients with history of severe toxicity to d-penicillamine.

Additional pediatric use information is approved for Mission Pharmacal Company's Thiola

EC (tiopronin delayed-release) tablets. However, due to Mission Pharmacal Company's marketing exclusivity rights, this drug product is not labeled with that information.

2.3 Monitoring

Measure urinary cystine 1 month after starting tiopronin delayed-release tablets and every 3 months thereafter. Adjust tiopronin delayed-release tablets dosage to maintain urinary cystine concentration less than 250 mg/L.

Assess for proteinuria before treatment and every 3 to 6 months during treatment *[see Warnings and Precautions (5.1)]*.

Discontinue tiopronin delayed-release tablets in patients who develop proteinuria, and monitor urinary protein and renal function. Consider restarting tiopronin delayed-release tablets treatment at a lower dosage after resolution of proteinuria.

3 DOSAGE FORMS AND STRENGTHS

Tablets for oral use:
100 mg tablets: White to off-white, round shaped, enteric coated tablets imprinted with "1A" with black ink on one side and plain on other side, free from physical defects.
300 mg tablets: White to off-white, round shaped, enteric coated tablets imprinted with "3A" with black ink on one side and plain on other side, free from physical defects.

4 CONTRAINDICATIONS

Tiopronin delayed-release tablets are contraindicated in patients with hypersensitivity to tiopronin or any other components of tiopronin delayed-release tablets *[see Warnings and Precautions (5.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Proteinuria

Proteinuria, including nephrotic syndrome, and membranous nephropathy, have been reported with tiopronin use. Pediatric patients receiving greater than 50 mg/kg of tiopronin per day may be at increased risk for proteinuria. *[see Dosage and Administration (2.3), Adverse Reactions (6.1, 6.2) Use in Specific Populations (8.4)]*. Monitor patients for the development of proteinuria and discontinue therapy in patients who develop proteinuria *[see Dosage and Administration (2.3)]*.

5.2 Hypersensitivity Reactions

Hypersensitivity reactions (drug fever, rash, fever, arthralgia and lymphadenopathy) have been reported *[see Contraindications (4)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Proteinuria *[see Warnings and Precautions (5.1)]*
- Hypersensitivity *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the adverse reaction rates observed in the clinical trials of the drug cannot be directly compared to

rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse reactions occurring at an incidence of ≥5% in an uncontrolled trial in 66 patients with cystinuria age 9 to 68 years are shown in the table below. Patients in group 1 had previously been treated with d-penicillamine; those in group 2 had not. Of those patients who had stopped taking d-penicillamine due to toxicity (34 out of 49 patients in group 1), 22 were able to continue treatment with tiopronin. In those without prior history of d-penicillamine treatment, 6% developed reactions of sufficient severity to require tiopronin withdrawal.

Table 1 presents adverse reactions ≥5% in either treatment group occurring in this trial.

Table 1: Adverse Reactions Occurring in One or More Patients

System Organ Class	Adverse Reaction	Group 1 Previously treated with d-penicillamine (N = 49)	Group 2 Naïve to d-penicillamine (N = 17)
Blood and Lymphatic System Disorders	anemia	1 (2%)	1 (6%)
Gastrointestinal Disorders	nausea	12 (25%)	2 (12%)
	emesis	5 (10%)	–
	diarrhea/soft stools	9 (18%)	1 (6%)
	abdominal pain	–	1 (6%)
	oral ulcers	6 (12%)	3 (18%)
General Disorders and Administration Site Conditions	fever	4 (8%)	–
	weakness	2 (4%)	2 (12%)
	fatigue	7 (14%)	–
	peripheral (edema)	3 (6%)	1 (6%)
	chest pain	–	1 (6%)
Metabolism and Nutrition Disorders	anorexia	4 (8%)	–
Musculoskeletal and Connective Tissue Disorders	arthralgia	–	2 (12%)
Renal and Urinary Disorders	proteinuria	5 (10%)	1 (6%)
	impotence	–	1 (6%)
Respiratory, Thoracic and Mediastinal Disorders	cough	–	1 (6%)
Skin and Subcutaneous Tissue Disorders	rash	7 (14%)	2 (12%)
	ecchymosis	3 (6%)	–

	pruritus	2 (4%)	1 (6%)
	urticaria	4 (8%)	–
	skin wrinkling	3 (6%)	1 (6%)

Taste Disturbance

A reduction in taste perception may develop. It is believed to be the result of chelation of trace metals by tiopronin. Hypogeusia is often self-limited.

6.2 Postmarketing Experience

Adverse reactions have been reported from the literature, as well as during post-approval use of tiopronin. Because the post-approval reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to tiopronin exposure.

Adverse reactions reported during the postmarketing use of tiopronin are listed by body system in **Table 2**.

Table 2: Adverse Reactions Reported for Tiopronin Pharmacovigilance by System Organ Class and Preferred Term

System Organ Class	Preferred Term
Cardiac Disorders	congestive heart failure
Ear and Labyrinth Disorder	vertigo
Gastrointestinal Disorders	abdominal discomfort; abdominal distension; abdominal pain; chapped lips; diarrhea; dry mouth; dyspepsia; eructation; flatulence; gastrointestinal disorder; gastroesophageal reflux disease; nausea; vomiting; jaundice; liver transaminitis
General Disorders and Administration Site Conditions	asthenia; chest pain; fatigue; malaise; pain; peripheral swelling; pyrexia; swelling
Investigations	glomerular filtration rate decreased; weight increased
Metabolism and Nutrition Disorders	decreased appetite; dehydration; hypophagia
Musculoskeletal and Connective Tissue Disorders	arthralgia; back pain; flank pain; joint swelling; limb discomfort; musculoskeletal discomfort; myalgia; neck pain; pain in extremity
Nervous System Disorders	ageusia; burning sensation; dizziness; dysgeusia; headache; hypoesthesia
Renal and Urinary Disorders	nephrotic syndrome; proteinuria; renal failure
Skin and Subcutaneous Tissue Disorders	dry skin; hyperhidrosis; pemphigus foliaceus; pruritus; rash; rash pruritic; skin irritation; skin texture abnormal; skin wrinkling; urticaria

7 DRUG INTERACTIONS

7.1 Alcohol

Tiopronin is released faster from tiopronin delayed-release tablets in the presence of alcohol and the risk for adverse events associated with tiopronin delayed-release tablets when taken with alcohol is unknown. Avoid alcohol consumption 2 hours before and 3 hours after taking tiopronin delayed-release tablets *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available published case report data with tiopronin have not identified a drug-associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes. Renal stones in pregnancy may result in adverse pregnancy outcomes *(see Clinical Considerations)*. In animal reproduction studies, there were no adverse developmental outcomes with oral administration of tiopronin to pregnant mice and rats during organogenesis at doses up to 2 times a 2 grams/day human dose (based on mg/m^2). The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies are 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Renal stones in pregnancy may increase the risk of adverse pregnancy outcomes, such as preterm birth and low birth weight.

Data

Animal Data

No findings of fetal malformations could be attributed to the drug in reproduction studies in mice and rats at doses up to 2 times the highest recommended human dose of 2 grams/day (based on mg/m^2).

8.2 Lactation

Risk Summary

There are no data on the presence of tiopronin in either human or animal milk or on the effects of the breastfed child. A published study suggests that tiopronin may suppress milk production. Because of the potential for serious adverse reactions, including nephrotic syndrome, advise patients that breastfeeding is not recommended during treatment with tiopronin delayed-release tablets.

8.4 Pediatric Use

Tiopronin delayed-release tablets are indicated in pediatric patients 9 years of age and older with severe homozygous cystinuria, in combination with high fluid intake, alkali, and diet modification, for the prevention of cystine stone formation who are not responsive to these measures alone. This indication is based on safety and efficacy data from a trial in patients 9 years to 68 years of age and clinical experience.

Proteinuria, including nephrotic syndrome, has been reported in pediatric patients. Pediatric patients receiving greater than 50 mg/kg tiopronin per day may be at greater risk *[see Dosage and Administration (2.1, 2.3), Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

Tiopronin delayed-release tablets are not approved for use in pediatric patients weighing

less than 20 kg or in pediatric patients unable to swallow tablets *[see Dosage and Administration (2.1)]*.

Additional pediatric use information is approved for Mission Pharmacal Company's Thiola EC (tiopronin delayed-release) tablets. However, due to Mission Pharmacal Company's marketing exclusivity rights, this drug product is not labeled with that information.

8.5 Geriatric Use

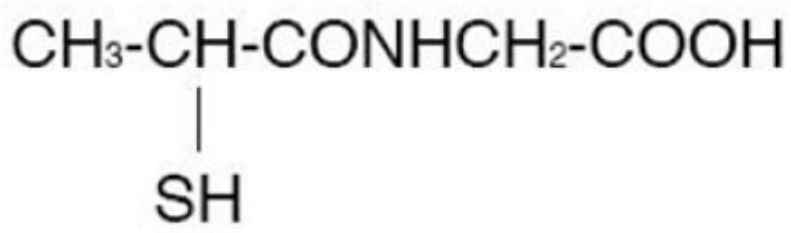
This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

10 OVERDOSAGE

There is no information on overdosage with tiopronin.

11 DESCRIPTION

Tiopronin delayed-release tablets are a reducing and cystine-binding thiol drug (CBTD) for oral use. Tiopronin is N-(2-Mercaptopropionyl) glycine and has the following structure:



Tiopronin has the empirical formula $C_5H_9NO_3S$ and a molecular weight of 163.19. In this drug product tiopronin exists as a dl racemic mixture.

Tiopronin is a white to off-white color crystalline powder, which is freely soluble in water.

Each tiopronin delayed-release tablet contains 100 or 300 mg of tiopronin. The inactive ingredients in tiopronin delayed-release tablets include lactose monohydrate, low substitute hydroxypropyl cellulose, hydroxypropyl cellulose, magnesium stearate, hypromellose 2910, methacrylic acid: ethyl acrylate copolymer (Eudragit L 100-55), talc, triethyl citrate. The imprinting ink contains shellac, ferrosoferric oxide and propylene glycol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The goal of therapy is to reduce urinary cystine concentration below its solubility limit. Tiopronin is an active reducing agent which undergoes thiol-disulfide exchange with cystine to form a mixed disulfide of tiopronin-cysteine. From this reaction, a water-soluble mixed disulfide is formed and the amount of sparingly soluble cystine is reduced.

12.2 Pharmacodynamics

The decrement in urinary cystine produced by tiopronin is generally proportional to the dose. A reduction in urinary cystine of 250 to 350 mg/day at tiopronin dosage of 1 g/day, and a decline of approximately 500 mg/day at a dosage of 2 g/day, might be expected. Tiopronin has a rapid onset and offset of action, showing a fall in cystine excretion on the first day of administration and a rise on the first day of drug withdrawal.

12.3 Pharmacokinetics

Absorption

Tiopronin Delayed-Release Tablets

When tiopronin IR and tiopronin delayed-release tablets single doses were given to fasted healthy subjects, the median time to peak plasma levels (T_{max}) was 1 (range: 0.5 to 2.1) and 3 (range: 1.0 to 6.0) hours, respectively. The peak exposure (C_{max}) and total exposure (AUC_{0-t}) of tiopronin from tiopronin delayed-release tablets were decreased by 22% and 7% respectively compared to tiopronin IR tablets.

Elimination

Excretion

When tiopronin is given orally, up to 48% of dose appears in urine during the first 4 hours and up to 78% by 72 hours.

Drug Interactions

Alcohol

An *in vitro* dissolution study was conducted to evaluate the impact of alcohol (5, 10, 20, and 40%) on the dose dumping of tiopronin delayed- release tablets. The study results showed that the addition of alcohol to the dissolution media increases the dissolution rate of tiopronin delayed- release tablets in the acidic media of 0.1N HCl *[see Drug Interactions (7.1)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term carcinogenicity studies in animals have not been performed.

Mutagenesis

Tiopronin was not genotoxic in the chromosomal aberration, sister chromatid exchange, and *in vivo* micronucleus assays.

Impairment of Fertility

High doses of tiopronin in experimental animals have been shown to interfere with maintenance of pregnancy and viability of the fetus. In 2 published male fertility studies in rats, tiopronin at 20 mg/kg/day intramuscular (IM) for 60 days induced reductions in testis, epididymis, vas deferens, and accessory sex glands weights and in the count and motility of cauda epididymal sperm.

16 HOW SUPPLIED/STORAGE AND HANDLING

100 mg delayed-release, white to off-white, round shaped, enteric-coated tablets imprinted with "1A" with black ink on one side and plain on other side, free from physical defects.

Bottles of 300 with child-resistant closure, **NDC** 13668-691-03.

300 mg delayed-release, white to off-white, round shaped, enteric-coated tablets imprinted with "3A" with black ink on one side and plain on other side, free from physical defects.

Bottles of 90 with child-resistant closure, **NDC** 13668-692-90.

Store at 25°C (77°F); excursions permitted between 15C° and 30°C (59°F and 86°F) *[see USP Controlled Room Temperature]*.

17 PATIENT COUNSELING INFORMATION

Lactation

Advise women that breastfeeding is not recommended during treatment with tiopronin delayed-release tablets *[see Use in Specific Populations (8.2)]*.

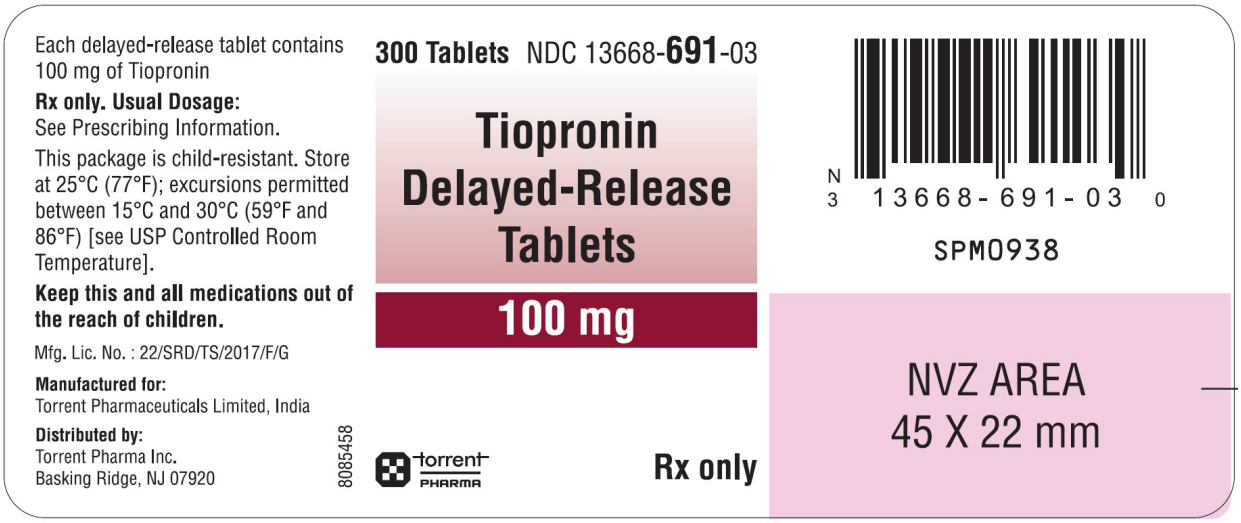
Manufactured for:
Torrent Pharmaceuticals Limited, India

Distributed by:
Torrent Pharma Inc., Basking Ridge, NJ 07920

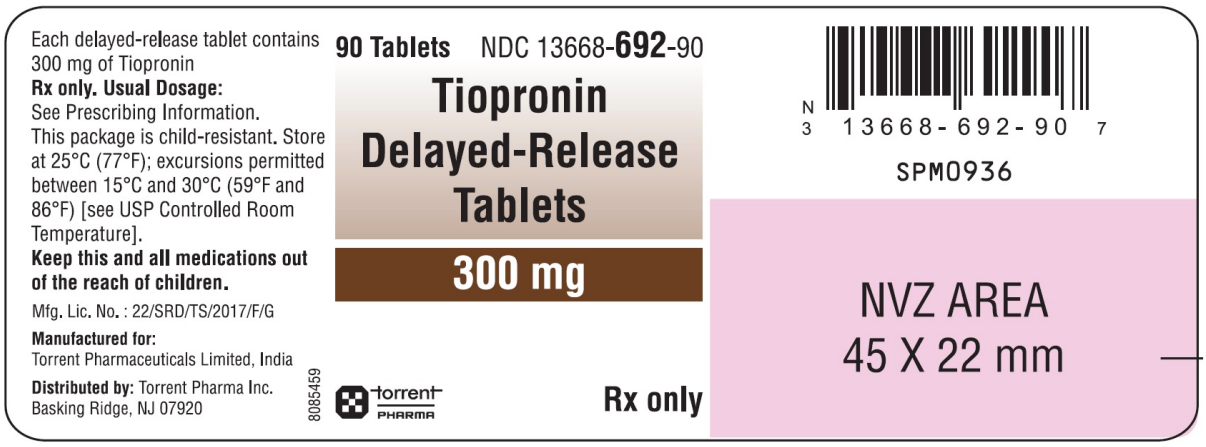
8088451 Revised: June 2023

PRINCIPAL DISPLAY PANEL

100 mg - 300 Tablets



300 mg - 90 Tablets



TIOPRONIN

tiopronin tablet, delayed release

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:13668-691
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
TIOPRONIN (UNII: C5W04GO61S) (TIOPRONIN - UNII:C5W04GO61S)	TIOPRONIN	100 mg

Inactive Ingredients	
Ingredient Name	**Strength**
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
HYDROXYPROPYL CELLULOSE, UNSPECIFIED (UNII: 9XZ8H6N6OH)	
HYDROXYPROPYL CELLULOSE, LOW SUBSTITUTED (UNII: 2165RE0K14)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
METHACRYLIC ACID - ETHYL ACRYLATE COPOLYMER (1:1) TYPE A (UNII: NX76LV5T8J)	
TALC (UNII: 7SEV7J4R1U)	
TRIETHYL CITRATE (UNII: 8Z96QXD6UM)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	

Product Characteristics			
Color	WHITE	**Score**	no score
Shape	ROUND	**Size**	8mm
Flavor		**Imprint Code**	1A
Contains			

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:13668-691-03	300 in 1 BOTTLE; Type 0: Not a Combination Product	01/30/2024	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA216990	01/30/2024	

TIOPRONIN

tiopronin tablet, delayed release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:13668-692
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
TIOPRONIN (UNII: C5W04GO61S) (TIOPRONIN - UNII:C5W04GO61S)	TIOPRONIN	300 mg

Inactive Ingredients

Ingredient Name	Strength
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
HYDROXYPROPYL CELLULOSE, UNSPECIFIED (UNII: 9XZ8H6N6OH)	
HYDROXYPROPYL CELLULOSE, LOW SUBSTITUTED (UNII: 2165RE0K14)	
HYPROMELLOSE, UNSPECIFIED (UNII: 3NXW29V3WO)	
METHACRYLIC ACID - ETHYL ACRYLATE COPOLYMER (1:1) TYPE A (UNII: NX76LV5T8J)	
TALC (UNII: 7SEV7J4R1U)	
TRIETHYL CITRATE (UNII: 8Z96QXD6UM)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	

Product Characteristics

Color	WHITE	**Score**	no score
Shape	ROUND	**Size**	11mm
Flavor		**Imprint Code**	3A
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:13668-692-90	90 in 1 BOTTLE; Type 0: Not a Combination Product	01/30/2024	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA216990	01/30/2024	

Labeler - Torrent Pharmaceuticals Limited (916488547)

Registrant - Torrent Pharma, Inc. (790033935)

Establishment

Name	Address	ID/FEI	Business Operations
Optimus Pharma Private Limited		675474672	MANUFACTURE(13668-692, 13668-691)

Revised: 2/2024

Torrent Pharmaceuticals Limited