

**L-GLUTAMINE - l-glutamine powder, for solution**  
**ANI Pharmaceuticals, Inc.**

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**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use L-GLUTAMINE ORAL POWDER safely and effectively. See full prescribing information for L-GLUTAMINE ORAL POWDER.

L-GLUTAMINE, oral powder

Initial U.S. Approval: 2017

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**INDICATIONS AND USAGE**  
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L-glutamine is an amino acid indicated to reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older. (1) (1)

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**DOSAGE AND ADMINISTRATION**  
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- 5 grams to 15 grams orally, twice daily based on body weight. (2)
- Each dose of L-glutamine should be mixed in 8 oz. (240 mL) of cold or room temperature beverage or 4 oz. to 6 oz. of food before ingestion. (2)

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**DOSAGE FORMS AND STRENGTHS**  
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Oral Powder: 5 grams of L-glutamine powder per foil-plastic laminate packet. (3) (3)

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**CONTRAINDICATIONS**  
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None (4) (4)

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**ADVERSE REACTIONS**  
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Most common adverse reactions (incidence > 10%) are constipation, nausea, headache, abdominal pain, cough, pain in extremity, back pain, and chest pain. (6) (5)

To report SUSPECTED ADVERSE REACTIONS, contact Novitium Pharma LLC at 1-855-204-1431 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch). (5)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 7/2024

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

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS & USAGE

L-glutamine is indicated to reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older.

### 2 DOSAGE & ADMINISTRATION

#### 2.1 Dosage

Administer L-glutamine orally, twice per day at the dose based on body weight according to Table 1.

**Table 1. Recommended Dosing**

Weight in kilograms	Weight in pounds	Per dose in grams	Per day in grams	Packets per dose	Packets per day
less than 30	less than 66	5	10	1	2
30 to 65	66 to 143	10	20	2	4
greater than 65	greater than 143	15	30	3	6

#### 2.2 Preparation of Product

Mix L-glutamine immediately before ingestion with 8 oz. (240 mL) of cold or room temperature beverage, such as water, milk or apple juice, or 4 oz. to 6 oz. of food such as applesauce or yogurt. Complete dissolution is not required prior to administration.

### 3 DOSAGE FORMS & STRENGTHS

Oral Powder: 5 grams of L-glutamine as a white to off-white colored powder filled in foil-plastic laminate packets.

### 4 CONTRAINDICATIONS

None

### 6 ADVERSE REACTIONS

#### 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.

The data described below reflect exposure to L-glutamine in 187 patients, including 136 exposed for 6 months and 109 exposed for  $\geq 1$  year. L-glutamine was studied in 2 placebo-controlled clinical trials (a phase 3 study, n=230 and a phase 2 study, n=70). In these trials, patients with sickle cell anemia or sickle  $\beta^0$ -thalassemia were randomized to receive L-glutamine (n=187) or placebo (n=111) orally twice daily for 48 weeks followed

by 3 weeks of tapering. Both studies included pediatric and adult patients (5-58 years of age) and 54% were female. The majority of patients were black (97.3%), had a diagnosis of sickle cell anemia (89.9%) and were receiving hydroxyurea at baseline (63.4%).

Treatment discontinuation due to adverse reactions was reported in 2.7% (n=5) of patients receiving L-glutamine. These adverse reactions included one case each of hypersplenism, abdominal pain, dyspepsia, burning sensation, and hot flash.

Serious adverse reactions were reported in both treatment groups, more frequently in the placebo group, and were consistent with the underlying disease.

Three deaths (3/187=1.6%) occurred during the study in the L-glutamine treatment group as compared to none in the placebo treatment group. None of the deaths were considered to be related to L-glutamine treatment. Adverse reactions occurring in greater than 10% of patients treated with L-glutamine are shown in Table 2 below.

**Table 2. Adverse Reactions Occurring at an Incidence > 10% in Clinical Studies of L-glutamine**

<b>Adverse reaction</b>	<b>L-glutamine N = 187 (%)</b>	<b>Placebo N = 111 (%)</b>
Constipation	21	18
Nausea	19	14
Headache	18	15
Abdominal Pain*	17	16
Cough	16	14
Pain in extremity	13	7
Back pain	12	5
Chest pain	12	8

\*Abdominal pain = abdominal pain and abdominal pain, upper

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

There are no available data on L-glutamine use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. Animal reproduction studies were not conducted with L-glutamine.

Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

### **8.2 Lactation**

#### Risk Summary

There are no data on the presence of L-glutamine in human milk, the effect on the breastfed infant or the effect on milk production. The developmental and health benefits from breastfeeding should be considered along with the mother's clinical need for L-

glutamine and any potential adverse effects on the breastfed child from L-glutamine or from the underlying maternal condition.

#### **8.4 Pediatric Use**

The safety and effectiveness of L-glutamine have been established in pediatric patients 5 years and older. Use of L-glutamine is supported by evidence from 2 placebo-controlled studies in adult and pediatric patients with sickle cell disease. The clinical studies enrolled 110 pediatric patients in the following age groups: 46 children (5 years up to less than 12 years) and 64 adolescents (12 years to less than 17 years).

The safety and effectiveness of L-glutamine in pediatric patients with sickle cell disease younger than 5 years old has not been established.

#### **8.5 Geriatric Use**

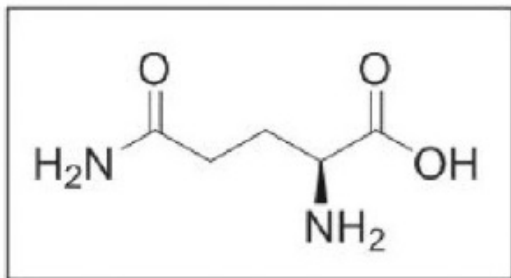
Clinical studies of L-glutamine did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose 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.

### **10 OVERDOSAGE**

Single oral doses of L-glutamine at about 20 g/kg to 22 g/kg, 8 g/kg to 11 g/kg, and 19 g/kg were lethal in mice, rats, and rabbits, respectively. Supportive measures should be undertaken in the event of overdose of L-glutamine.

### **11 DESCRIPTION**

L-glutamine is an amino acid. L-glutamine is designated chemically as (S)-2-aminoglutaramic acid, L-glutamic acid 5-amide, or (S)-2,5-diamino-5-oxopentanoic acid. The molecular formula is  $C_5H_{10}N_2O_3$  with the molecular weight of 146.15 g/mol and the following structural formula:



L-glutamine Oral Powder is formulated as a white to off-white colored powder and is packaged as 5 grams in a foil-plastic laminate packet for oral administration.

### **12 CLINICAL PHARMACOLOGY**

#### **12.1 Mechanism of Action**

The mechanism of action of the amino acid L-glutamine in treating sickle cell disease (SCD) is not fully understood. Oxidative stress phenomena are involved in the pathophysiology of SCD. Sickle red blood cells (RBCs) are more susceptible to oxidative

damage than normal RBCs, which may contribute to the chronic hemolysis and vaso-occlusive events associated with SCD. The pyridine nucleotides, NAD<sup>+</sup> and its reduced form NADH, play roles in regulating and preventing oxidative damage in RBCs. L-glutamine may improve the NAD redox potential in sickle RBCs through increasing the availability of reduced glutathione.

## **12.2 Pharmacodynamics**

In vivo analyses demonstrated that L-glutamine supplementation improved NAD redox potential.

## **12.3 Pharmacokinetics**

The pharmacokinetics of L-glutamine has been studied in healthy subjects and a variety of disease states. Relevant results from published literature are summarized below.

### Absorption

Following single-dose oral administration of L-glutamine at 0.1 g/kg, mean peak L-glutamine concentration was 1028 µM (or 150 mcg/mL) occurring approximately 30 minutes after administration. The pharmacokinetics following multiple oral doses has not been characterized.

### Distribution

After an intravenous (IV) bolus dose, the volume of distribution was estimated to be approximately 200 mL/kg.

### Elimination

After an intravenous bolus dose, the terminal half-life of L-glutamine was approximately one hour.

### *Metabolism*

Endogenous L-glutamine participates in various metabolic activities, including the formation of glutamate, and synthesis of proteins, nucleotides, and amino sugars. Exogenous L-glutamine is anticipated to undergo similar metabolism.

### *Excretion*

Metabolism is the major route of elimination for L-glutamine. Although L-glutamine is eliminated by glomerular filtration, it is almost completely reabsorbed by the renal tubules.

### Specific Populations

The safety of L-glutamine has not been established in patients with renal or hepatic impairment.

### Drug Interactions

No drug interaction studies have been conducted.

## **13 NONCLINICAL TOXICOLOGY**

### **13.1 Carcinogenesis & Mutagenesis & Impairment Of Fertility**

Long-term studies in animals have not been performed to evaluate the carcinogenic

potential of L-glutamine.

L-glutamine was not mutagenic in a bacterial mutagenicity (Ames) assay, nor clastogenic in a chromosome aberration assay in mammalian (Chinese Hamster Lung CHL/IU) cells.

Animal reproduction studies and its potential for impairment of fertility have not been conducted with L-glutamine. It is also not known whether L-glutamine can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity.

## 14 CLINICAL STUDIES

The efficacy of L-glutamine in sickle cell disease was evaluated in a randomized, double-blind, placebo-controlled, multi-center clinical trial entitled "A Phase III Safety and Efficacy Study of L-Glutamine to Treat Sickle Cell Disease or Sickle  $\beta^0$ -thalassemia" [NCT01179217] (see Table 3).

The clinical trial evaluated the efficacy and safety of L-glutamine in 230 patients (5 to 58 years of age) with sickle cell anemia or sickle  $\beta^0$ -thalassemia who had 2 or more painful crises within 12 months prior to enrollment. Eligible patients stabilized on hydroxyurea for at least 3 months continued their therapy throughout the study. The trial excluded patients who had received blood products within 3 weeks, had renal insufficiency or uncontrolled liver disease, or were pregnant (or planning pregnancy) or lactating. Study patients received L-glutamine or placebo for a treatment duration of 48 weeks followed by 3 weeks of tapering.

Efficacy was demonstrated by a reduction in the number of sickle cell crises through Week 48 and prior to the start of tapering among patients that received L-glutamine compared to patients who received placebo. This clinical benefit was observed irrespective of hydroxyurea use. A sickle cell crisis was defined as a visit to an emergency room/medical facility for sickle cell disease-related pain which was treated with a parenterally administered narcotic or parenterally administered ketorolac. In addition, the occurrence of chest syndrome, priapism, and splenic sequestration were considered sickle cell crises. Treatment with L-glutamine also resulted in fewer hospitalizations due to sickle cell pain at Week 48, fewer cumulative days in hospital and a lower incidence of acute chest syndrome.

**Table 3. Results from the L-glutamine Clinical Trial in Sickle Cell Disease**

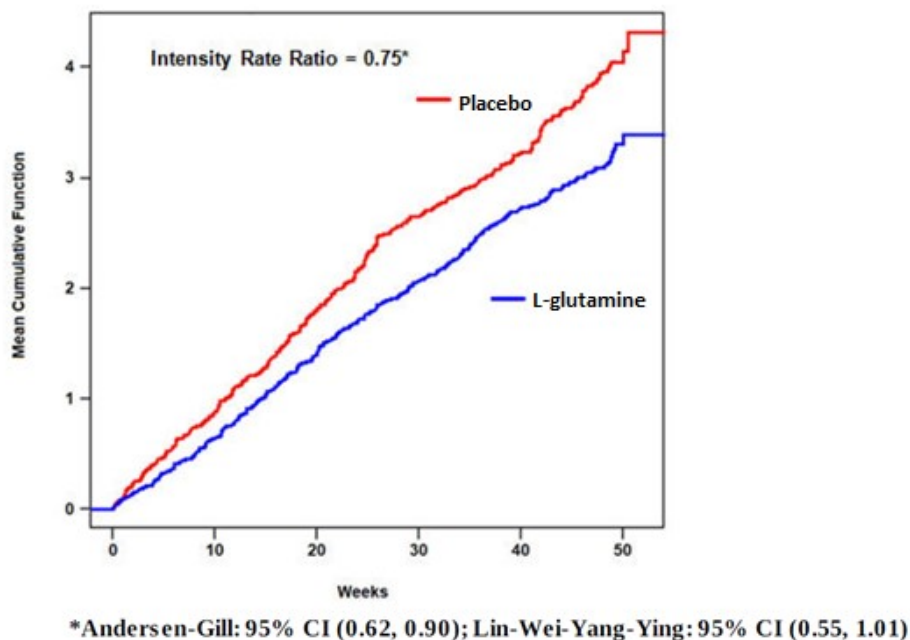
<b>Event</b>	<b>L-glutamine (n = 152)</b>	<b>Placebo (n = 78)</b>
Median number of sickle cell crises (min, max)*	3 (0, 15)	4 (0, 15)
Median number of hospitalizations for sickle cell pain (min, max)*	2 (0, 14)	3 (0, 13)
Median cumulative days hospitalized (min, max)*	6.5 (0, 94)	11 (0, 187)
Median time (days) to first sickle cell crisis (95% CI)*,†	84 (62, 109)	54 (31, 73)
Patients with occurrences of acute chest syndrome (%)*	13 (8.6%)	18 (23.1%)

\*Measured through 48 weeks of treatment

†Hazard Ratio=0.69 (95% CI=0.52, 0.93), estimated based on unstratified Cox's proportional model. Median time and 95% CI were estimated based on the Kaplan Meier method.

The recurrent crisis event time analysis (Figure 1) yielded an intensity rate ratio (IRR) value of 0.75 with 95% CI= (0.62, 0.90) and (0.55, 1.01) based on unstratified models using the Andersen-Gill and Lin, Wei, Yang and Ying methods, respectively in favor of L-glutamine, suggesting that over the entire 48-week period, the average cumulative crisis count was reduced by 25% from the L-glutamine group over the placebo group.

Figure 1. Recurrent Event Time for Sickle Cell Crises by Treatment Group



## 16 HOW SUPPLIED/STORAGE AND HANDLING

L-glutamine Oral Powder is supplied in foil-plastic laminate packets containing 5 grams of L-glutamine white to off-white colored powder.

- Carton of 60 packets: NDC 70954-417-20

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

## 17 PATIENT COUNSELING INFORMATION

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

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### Dosage and Administration

Advise patient to take a missed dose as soon as they remember. Patient should not double the dose that they take.

Instruct patient to mix each dose in 8 oz. (240 mL) of cold or room temperature beverage or 4 to 6 oz. of food.

Advise patient that complete dissolution is not required prior to administration.

Manufactured by:

**Novitium Pharma LLC**

70 Lake Drive, East Windsor

New Jersey 08520

**Issued:** 02/2024

LB4394-01

**SPL PATIENT PACKAGE INSERT**

**INSTRUCTIONS FOR USE**

L-glutamine (l-gloo' ta meen)

Oral Powder

Read this Instructions for Use before you start taking L-glutamine and each time you get a refill. There may be new information. This Instructions for Use does not take the place of talking to your healthcare provider about your medical condition or treatment. You and your healthcare provider should talk about L-glutamine before you start taking it and at regular checkups.

L-glutamine is usually taken 2 times a day. Take L-glutamine as prescribed by your healthcare provider.

**You will need the following supplies to mix and take L-glutamine:**

- Your prescribed dose of L-glutamine (1, 2, or 3 packets as directed by your healthcare provider).
- a clean cup or small bowl
- a spoon



**You can mix L-glutamine:**

- with a liquid, such as water, milk, or apple juice **Or**
- with food, such as applesauce or yogurt

**How to mix and take a dose of L-glutamine.**

	<b>Mixing with Liquid</b>	<b>Mixing with Food</b>
<b>Step 1:</b>		



Fill a cup with 8 ounces (240 mL) of liquid or a small bowl with 4 to 6 ounces of food.

The food or liquid should be cold or room temperature.

**Do not** use a hot food or liquid.



**Step 2:**

Tear open the L-glutamine packet at the top.



**Step 3:**

Pour the contents of the L-glutamine packet into the cup or bowl.

If more than 1 packet is needed, repeat steps 2 and 3 above for all of the packets needed to prepare your prescribed doses of L-glutamine.



**Step 4:**

Use the spoon to mix the prescribed dose of L-glutamine with the liquid or food.

L-glutamine may not fully dissolve. You can take your dose of L-glutamine even if it does not fully dissolve.



**Step 5:**

Drink or eat the prescribed dose of L-glutamine right away after mixing it.

**Do not** store the L-glutamine mixture for later use.



If you miss a dose of L-glutamine, take the missed dose as soon as you remember. **Do not** double the dose to make up for a missed dose.

**How should I store L-glutamine?**

- Store L-glutamine at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep L-glutamine away from direct sunlight.

**Keep L-glutamine and all medicines out of the reach of children.**

Manufactured by:

**Novitium Pharma LLC**

70 Lake Drive, East Windsor

New Jersey 08520

**Issued:** 02/2024

LB4394-01

For more information call 1-855-204-1431.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

**PACKAGE LABEL.PRINCIPAL DISPLAY PANEL**

Packet Label for L-Glutamine Oral Powder, 5g/Packet

NDC 70954-417-10

# L-glutamine Oral Powder

**5 Grams**


Mix the contents of this packet with cold or room temperature beverage or food immediately before dosing.

Administer the prescribed amount orally, twice daily, taking no more than 6 packets per day.

Package is not child resistant.

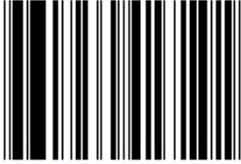
Keep this and all drugs out of the reach of children.

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

 **Rx only**

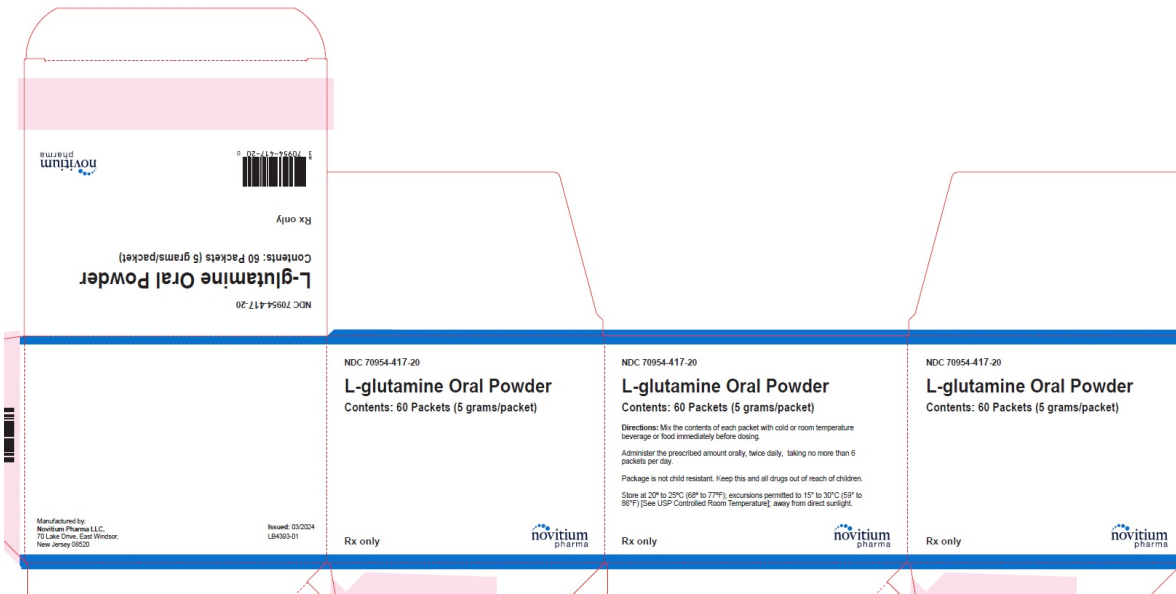
Manufactured by:  
**Novitium Pharma LLC**  
70 Lake Drive, East Windsor  
New Jersey 08520

**Issued:** 02/2024      LB4392-01



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3 70954-417-10 1

Carton Label for L-Glutamine Oral Powder, 60 packets/carton



## L-GLUTAMINE

l-glutamine powder, for solution

### Product Information

<b>Product Type</b>	HUMAN PRESCRIPTION DRUG	<b>Item Code (Source)</b>	NDC:70954-417
<b>Route of Administration</b>	ORAL		

### Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
GLUTAMINE (UNII: 0RH81L854J) (GLUTAMINE - UNII:0RH81L854J)	GLUTAMINE	5 g

### Product Characteristics

<b>Color</b>	WHITE (white to off-white)	<b>Score</b>	
<b>Shape</b>		<b>Size</b>	
<b>Flavor</b>		<b>Imprint Code</b>	
<b>Contains</b>			

### Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:70954-417-20	60 in 1 CARTON	07/11/2024	
1	NDC:70954-417-10	1 in 1 PACKET; Type 0: Not a Combination Product		

### Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA215647	07/11/2024	

**Labeler** - ANI Pharmaceuticals, Inc. (145588013)

<b>Establishment</b>			
<b>Name</b>	<b>Address</b>	<b>ID/FEI</b>	<b>Business Operations</b>
Novitium Pharma LLC		080301870	ANALYSIS(70954-417) , LABEL(70954-417) , MANUFACTURE(70954-417) , PACK(70954-417)

Revised: 7/2022

ANI Pharmaceuticals, Inc.