

**CENTER FOR DRUG EVALUATION AND  
RESEARCH AND CENTER FOR BIOLOGICS  
EVALUATION AND RESEARCH**

*APPLICATION NUMBER:*

**125151/0**

**APPROVED LABELING**

CS

**ELAPRASE™ (idursulfase)**

Solution for intravenous infusion

**WARNING****Risk of hypersensitivity reactions.**

**Anaphylactoid reactions, which may be life threatening, have been observed in some patients during ELAPRASE infusions. Therefore, appropriate medical support should be readily available when ELAPRASE is administered. Patients with compromised respiratory function or acute respiratory disease may be at risk of serious acute exacerbation of their respiratory compromise due to infusion reactions, and require additional monitoring.**

**DESCRIPTION**

ELAPRASE is a formulation of idursulfase, a purified form of human iduronate-2-sulfatase, a lysosomal enzyme. Idursulfase is produced by recombinant DNA technology in a human cell line. Idursulfase is an enzyme that hydrolyzes the 2-sulfate esters of terminal iduronate sulfate residues from the glycosaminoglycans dermatan sulfate and heparan sulfate in the lysosomes of various cell types.

Idursulfase is a 525-amino acid glycoprotein with a molecular weight of approximately 76 kilodaltons. The enzyme contains eight asparagine-linked glycosylation sites occupied by complex oligosaccharide structures. The enzyme activity of idursulfase is dependent on the post-translational modification of a specific cysteine to formylglycine. Idursulfase has a specific activity ranging from 41 to 77 U/mg of protein (one unit is defined as the amount of enzyme required to hydrolyze 1  $\mu$ mole of heparin disaccharide substrate per hour under the specified assay conditions).

ELAPRASE is intended for intravenous infusion and is supplied as a sterile, nonpyrogenic clear to slightly opalescent colorless solution that must be diluted prior to administration in 0.9% Sodium Chloride Injection, USP. Each vial contains an extractable volume of 3.0 mL with an idursulfase concentration of 2.0 mg/mL at a pH of approximately 6, providing 6.0 mg idursulfase, 24.0 mg sodium chloride, 6.75 mg sodium phosphate monobasic monohydrate, 2.97 mg sodium phosphate dibasic heptahydrate, and 0.66 mg polysorbate 20. ELAPRASE does not contain preservatives; vials are for single use only.

**CLINICAL PHARMACOLOGY****Mechanism of Action**

Hunter syndrome (Mucopolysaccharidosis II, MPS II) is an X-linked recessive disease caused by insufficient levels of the lysosomal enzyme iduronate-2-sulfatase. This enzyme cleaves the terminal 2-*O*-sulfate moieties from the glycosaminoglycans (GAG) dermatan sulfate and heparan sulfate. Due to the missing or defective iduronate-2-sulfatase enzyme in patients with Hunter syndrome, GAG progressively accumulate in the lysosomes of a variety of cells, leading to cellular engorgement, organomegaly, tissue destruction, and organ system dysfunction.

Treatment of Hunter syndrome patients with ELAPRASE provides exogenous enzyme for

43 uptake into cellular lysosomes. Mannose-6-phosphate (M6P) residues on the oligosaccharide  
 44 chains allow specific binding of the enzyme to the M6P receptors on the cell surface, leading to  
 45 cellular internalization of the enzyme, targeting to intracellular lysosomes and subsequent  
 46 catabolism of accumulated GAG.

#### 47 Pharmacokinetics

48 The pharmacokinetic characteristics of idursulfase were evaluated in several studies in patients  
 49 with Hunter syndrome. The serum concentration of idursulfase was quantified using an antigen-  
 50 specific ELISA assay. The area under the concentration-time curve (AUC) increased in a greater  
 51 than dose proportional manner as the dose increased from 0.15 mg/kg to 1.5 mg/kg following a  
 52 single 1-hour infusion of ELAPRASE. The pharmacokinetic parameters at the recommended  
 53 dose regimen (0.5 mg/kg ELAPRASE administered weekly as a 3-hour infusion) were  
 54 determined at Week 1 and Week 27 in 10 patients ages 7.7 to 27 years (Table 1). There were no  
 55 apparent differences in PK parameter values between Week 1 and Week 27.  
 56

57 **Table 1 Pharmacokinetic Parameters (Mean, Standard Deviation)**

Pharmacokinetic Parameter	Week 1	Week 27
$C_{max}$ ( $\mu\text{g/mL}$ )	1.5 (0.6)	1.1 (0.3)
AUC ( $\text{min} \cdot \mu\text{g/mL}$ )	206 (87)	169 (55)
$t_{1/2}$ (min)	44 (19)	48 (21)
Cl ( $\text{mL/min/kg}$ )	3.0 (1.2)	3.4 (1.0)
$V_{ss}$ (% BW)	21 (8)	25 (9)

#### 58 CLINICAL STUDIES

59 The safety and efficacy of ELAPRASE were evaluated in a randomized, double-blind, placebo-  
 60 controlled clinical study of 96 patients with Hunter syndrome. The study included patients with  
 61 a documented deficiency in iduronate-2-sulfatase enzyme activity who had a percent predicted  
 62 forced vital capacity (%-predicted FVC) less than 80%. The patients' ages ranged from 5 to 31  
 63 years. Patients who were unable to perform the appropriate pulmonary function testing, or those  
 64 who could not follow protocol instructions were excluded from the study. Patients received  
 65 ELAPRASE 0.5 mg/kg every week (n=32), ELAPRASE 0.5 mg/kg every other week (n=32), or  
 66 placebo (n=32). The study duration was 53 weeks.

67 The primary efficacy outcome assessment was a two-component composite score based on the  
 68 sum of the ranks of the change from baseline to Week 53 in distance walked during a six-minute  
 69 walk test (6-MWT) and the ranks of the change in %-predicted FVC. This two-component  
 70 composite primary endpoint differed statistically significantly between the three groups, and the  
 71 difference was greatest between the placebo group and the weekly treatment group (weekly  
 72 ELAPRASE vs. placebo,  $p=0.0049$ ).

73 Examination of the individual components of the composite score showed that, in the adjusted  
 74 analysis, the weekly ELAPRASE-treated group experienced a 35 meter greater mean increase in  
 75 the distance walked in six minutes compared to placebo. The changes in %-predicted FVC were  
 76 not statistically significant (Table 2).

7 **Table 2 Clinical Study Results**

	ELAPRASE Weekly n=32 <sup>a</sup>			Placebo n=32 <sup>a</sup>			ELAPRASE Weekly – Placebo
	Baseline	Week 53	Change <sup>b</sup>	Baseline	Week 53	Change <sup>b</sup>	Difference in Change
<b>Results from the 6-Minute Walk Test (Meters)</b>							
Mean ± SD	392 ± 108	436 ± 138	44 ± 70	393 ± 106	400 ± 106	7 ± 54	37 ± 16 <sup>c</sup> 35 ± 14 <sup>d</sup> (p=0.01)
Median	397	429	31	403	412	-4	
Percentiles (25 <sup>th</sup> , 75 <sup>th</sup> )	316, 488	365, 536	0, 94	400, 469	361, 460	-30, 31	
<b>Results from the Forced Vital Capacity Test (% of Predicted)</b>							
Mean ± SD	55.3 ± 15.9	58.7 ± 19.3	3.4 ± 10.0	55.6 ± 12.3	56.3 ± 15.7	0.8 ± 9.6	2.7 ± 2.5 <sup>c</sup> 4.3 ± 2.3 <sup>d</sup> (p=0.07)
Median	54.9	59.2	2.1	57.4	54.6	-2.5	
Percentiles (25 <sup>th</sup> , 75 <sup>th</sup> )	43.6, 69.3	44.4, 70.7	-0.8; 9.5	46.9, 64.4	43.8, 67.5	-5.4, 5.0	
<sup>a</sup> One patient in the placebo group and one patient in the ELAPRASE group died before Week 53; imputation was by last observation carried forward in the intent-to-treat analysis <sup>b</sup> Change, calculated as Week 53 minus Baseline <sup>c</sup> Observed mean ± SE <sup>d</sup> ANCOVA model based mean ± SE, adjusted for baseline disease severity, region, and age.							

78 Measures of bioactivity were urinary GAG levels and changes in liver and spleen size. Urinary  
) GAG levels were elevated in all patients at baseline. Following 53 weeks of treatment, mean  
80 urinary GAG levels were markedly reduced in the ELAPRASE weekly group, although GAG  
81 levels still remained above the upper limit of normal in half of the ELAPRASE-treated patients.  
82 Urinary GAG levels remained elevated and essentially unchanged in the placebo group.  
83 Sustained reductions in both liver and spleen volumes were observed in the ELAPRASE weekly  
84 group through Week 53 compared to placebo. There were essentially no changes in liver and  
85 spleen volumes in the placebo group.

## 86 INDICATIONS AND USAGE

87 ELAPRASE is indicated for patients with Hunter syndrome (Mucopolysaccharidosis II, MPS II).  
88 ELAPRASE has been shown to improve walking capacity in these patients.

## 89 CONTRAINDICATIONS

90 None.

## 91 WARNINGS

### 92 Hypersensitivity Reactions (see **BOXED WARNING**)

93  
94 Hypersensitivity reactions, which may be life-threatening, have been observed in some patients  
95 during ELAPRASE infusions. Reactions have included respiratory distress, hypoxia,  
5 hypotension, angioedema, or seizure. In clinical trials with ELAPRASE, 16/108 patients (15%)  
97 experienced infusion reactions during 26 of 8274 infusions (0.3%) that involved adverse events  
98 in at least two of the following three body systems: cutaneous, respiratory, or cardiovascular. Of

99 these 16 patients, 11 experienced significant hypersensitivity reactions during 19 of 8274  
100 ) infusions (0.2%). One of these episodes occurred in a patient with a tracheostomy and severe  
101 airway disease, who received an ELAPRASE infusion while he had a pre-existing febrile illness,  
102 and then experienced respiratory distress, hypoxia, cyanosis, and seizure with loss of  
103 consciousness.

104  
105 Because of the potential for severe infusion reactions, appropriate medical support should be  
106 readily available when ELAPRASE is administered.

107  
108 When severe infusion reactions occurred during clinical studies, subsequent infusions were  
109 managed by use of antihistamines and/or corticosteroids prior to or during infusions, a slower  
110 rate of ELAPRASE administration, and/or early discontinuation of the ELAPRASE infusion if  
111 serious symptoms developed. With these measures, no patient discontinued treatment  
112 permanently due to a hypersensitivity reaction.

113  
114 Patients with compromised respiratory function or acute respiratory disease may be at higher risk  
115 of life-threatening complications from infusion reactions. Consider delaying the ELAPRASE  
116 infusion in patients with concomitant acute respiratory and/or febrile illness.

117  
118 If a severe infusion reaction occurs, immediately suspend the infusion of ELAPRASE and  
119 initiate appropriate treatment, depending on the severity of the symptoms. Consider resuming  
120 the infusion at slower rate, or, if the reaction is serious enough to warrant it, discontinue the  
121 ELAPRASE infusion for that visit.

## 122 **PRECAUTIONS**

### 123 **Information for Patients**

124 A Hunter Outcome Survey has been established in order to understand better the variability and  
125 progression of Hunter syndrome (MPS II) in the population as a whole, and to monitor and  
126 evaluate long-term treatment effects of ELAPRASE. Patients and their physicians are  
127 encouraged to participate in this program. For more information, visit [www.elaprase.com](http://www.elaprase.com) or call  
128 OnePath<sup>SM</sup> at 1-866-888-0660.

### 129 **Drug Interactions**

130 No formal drug interaction studies have been conducted with ELAPRASE.

### 131 **Carcinogenesis, Mutagenesis, Impairment of Fertility**

132 Long-term studies in animals to evaluate carcinogenic potential or studies to evaluate mutagenic  
133 potential have not been performed with ELAPRASE.

134 ELAPRASE at intravenous doses up to 5 mg/kg, administered twice weekly (about 1.6 times the  
135 recommended human weekly dose based on body surface area) had no effect on fertility and  
136 reproductive performance in male rats.

### 137 **Pregnancy: Teratogenic Effects: Category C**

3  
139 Reproduction studies in pregnant female animals have not been conducted with ELAPRASE. It  
is also not known whether ELAPRASE can cause fetal harm when administered to a pregnant

140 woman or can affect reproduction capacity. ELAPRASE should be given to pregnant women  
141 only if clearly needed.

### 142 **Nursing Mothers**

143 It is not known whether this product is excreted in human milk. Because many drugs are  
144 excreted in human milk, caution should be exercised when ELAPRASE is administered to a  
145 nursing woman.

### 146 **Pediatric Use**

147 Patients in the clinical studies were age five and older (see CLINICAL STUDIES). Children,  
148 adolescents, and adults responded similarly to treatment with ELAPRASE. Safety and efficacy  
149 have not been established in pediatric patients less than five years of age.

### 150 **Geriatric Use**

151 Clinical studies of ELAPRASE did not include patients aged 65 or over. It is not known whether  
152 geriatric patients respond differently from younger patients.

## 153 **ADVERSE REACTIONS**

154 The most common adverse reactions requiring intervention were infusion-related reactions (see  
155 BOXED WARNING and WARNINGS).

156  
157 In clinical studies, the most frequent serious adverse events related to the use of ELAPRASE  
158 were hypoxic episodes. Other notable serious adverse reactions that occurred in the ELAPRASE  
159 treated patients but not in the placebo patients included one case each of: cardiac arrhythmia,  
160 pulmonary embolism, cyanosis, respiratory failure, infection, and arthralgia.

161  
162 Adverse reactions were commonly reported in association with infusions. The most common  
163 infusion-related reactions were headache, fever, cutaneous reactions (rash, pruritus, erythema,  
164 and urticaria), and hypertension. The frequency of infusion-related reactions decreased over  
165 time with continued ELAPRASE treatment.

166  
167 Because clinical trials are conducted under widely varying conditions, adverse reaction rates  
168 observed in the clinical trials of a product cannot be directly compared to rates in the clinical  
169 trials of another product and may not reflect the rates observed in practice.

170  
171 Table 3 enumerates those adverse reactions that were reported during the 53-week, placebo-  
172 controlled study that occurred in at least 10% of patients treated with ELAPRASE weekly  
173 administration, and that occurred more frequently than in the placebo patients. The most  
174 common (>30%) adverse reactions were pyrexia, headache, and arthralgia.

175 **Table 3** **Summary of Adverse Reactions Occurring in at Least 10% of Patients**  
 5 **Treated with ELAPRASE Weekly in the 53-week Controlled Trial and**  
 177 **Occurring More Frequently than in the Placebo Group**  
 178

Adverse Event	ELAPRASE 0.5 mg/kg Weekly (n=32)	Placebo (n=32)
Pyrexia	20 (63%)	19 (59%)
Headache	19 (59%)	14 (44%)
Arthralgia	10 (31%)	9 (28%)
Limb pain	9 (28%)	8 (25%)
Pruritus	9 (28%)	5 (16%)
Hypertension	8 (25%)	7 (22%)
Malaise	7 (22%)	6 (19%)
Visual disturbance	7 (22%)	2 (6%)
Wheezing	6 (19%)	5 (16%)
Abscess	5 (16%)	0 (0%)
Musculoskeletal dysfunction NOS	5 (16%)	3 (9%)
Chest wall musculoskeletal pain	5 (16%)	0 (0%)
Urticaria	5 (16%)	0 (0%)
Superficial injury	4 (13%)	3 (9%)
Anxiety, irritability	4 (13%)	1 (3%)
Atrial abnormality	4 (13%)	3 (9%)
Adverse events resulting from injury	4 (13%)	2 (6%)
Dyspepsia	4 (13%)	0 (0%)
Infusion site edema	4 (13%)	3 (9%)
Skin disorder NOS	4 (13%)	1 (3%)
Pruritic rash	4 (13%)	0 (0%)

179

### 180 Immunogenicity

181 Fifty-one percent (32 of 63) of patients in the weekly ELAPRASE treatment arm in the clinical  
 182 study (53-week placebo-controlled study with an open-label extension) developed anti-  
 183 idursulfase IgG antibodies as assessed by ELISA or conformation specific antibody assay and  
 184 confirmed by radioimmunoprecipitation assay (RIP). Sera from 4 out of 32 RIP confirmed anti-  
 185 idursulfase antibody positive patients were found to neutralize idursulfase activity in vitro. The  
 186 incidence of antibodies that inhibit cellular uptake of idursulfase into cells is currently unknown,  
 187 and the incidence of IgE antibodies to idursulfase is not known. Patients who developed IgG  
 188 antibodies at any time had an increased incidence of infusion reactions, including  
 189 hypersensitivity reactions. The reduction of urinary GAG excretion was less in patients in whom  
 190 circulating anti-idursulfase antibodies were detected. The relationship between the presence of  
 191 anti-idursulfase antibodies and clinical efficacy outcomes is unknown.

192

193 The data reflect the percentage of patients whose test results were positive for antibodies to  
 194 idursulfase in specific assays, and are highly dependent on the sensitivity and specificity of these  
 195 assays. Additionally, the observed incidence of antibody positivity in an assay may be  
 196 influenced by several factors, including sample handling, timing of sample collection,  
 197 concomitant medication, and underlying disease. For these reasons, comparison of the incidence

198 of antibodies to idursulfase with the incidence of antibodies to other products may be misleading.

## 199 **OVERDOSAGE**

200 There is no experience with overdosage of ELAPRASE in humans. Single intravenous doses of  
201 idursulfase up to 20 mg/kg were not lethal in male rats and cynomolgus monkeys (approximately  
202 6.5 and 13 times, respectively, of the recommended human dose based on body surface area) and  
203 there were no clinical signs of toxicity.

## 204 **DOSAGE AND ADMINISTRATION**

205 The recommended dosage regimen of ELAPRASE is 0.5 mg/kg of body weight administered  
206 every week as an intravenous infusion.

207 ELAPRASE is a concentrated solution for intravenous infusion and must be diluted in 100 mL of  
208 0.9% Sodium Chloride Injection, USP. Each vial of ELAPRASE contains a 2.0 mg/mL solution  
209 of idursulfase protein (6.0 mg) in an extractable volume of 3.0 mL, and is for single use only.  
210 Use of an infusion set equipped with a 0.2 micrometer ( $\mu\text{m}$ ) filter is recommended.

211 The total volume of infusion may be administered over a period of 1 to 3 hours. Patients may  
212 require longer infusion times due to infusion reactions; however, infusion times should not  
213 exceed 8 hours (see STORAGE). The initial infusion rate should be 8 mL/hr for the first  
214 15 minutes. If the infusion is well tolerated, the rate may be increased by 8 mL/hr increments at  
215 15 minute intervals in order to administer the full volume within the desired period of time.  
216 However, at no time should the infusion rate exceed 100 mL/hr. The infusion rate may be  
7 slowed and/or temporarily stopped, or discontinued for that visit, based on clinical judgment, if  
.8 infusion reactions were to occur (see WARNINGS). ELAPRASE should not be infused with  
219 other products in the infusion tubing.

## 220 **Preparation and Administration Instructions: Use Aseptic Techniques**

221 ELAPRASE should be prepared and administered by a health care professional.

- 222 1. Determine the total volume of ELAPRASE to be administered and the number of vials  
223 needed based on the patient's weight and the recommended dose of 0.5 mg/kg.

$$224 \quad \text{Patient's weight (kg)} \times 0.5 \text{ mg per kg of ELAPRASE} \div 2 \text{ mg per mL} =$$
$$225 \quad \text{Total \# mL of ELAPRASE}$$

$$226 \quad \text{Total \# mL of ELAPRASE} \div 3 \text{ mL per vial} = \text{Total \# of vials}$$

227 Round up to determine the number of whole vials needed from which to withdraw the  
228 calculated volume of ELAPRASE to be administered.

- 229 2. Perform a visual inspection of each vial. ELAPRASE is a clear to slightly opalescent,  
230 colorless solution. Do not use if the solution in the vials is discolored or particulate  
231 matter is present. ELAPRASE should not be shaken.
- 232 3. Withdraw the calculated volume of ELAPRASE from the appropriate number of vials.
- 233 4. Dilute the total calculated volume of ELAPRASE in 100 mL of 0.9% Sodium Chloride  
234 Injection, USP. Once diluted into normal saline, the solution in the infusion bag should  
235 be mixed gently, but not shaken. Diluted solution should be discarded if not administered  
6 or refrigerated within 8 hours of preparation. Diluted solution may be stored refrigerated  
237 for up to 48 hours.

- 238 5. ELAPRASE is supplied in single-use vials. Remaining ELAPRASE left in a vial after  
9 withdrawing the patient's calculated dose should be disposed of in accordance with local  
240 requirements.

## 241 **STORAGE**

242 Store ELAPRASE vials under refrigeration at 2°C to 8°C (36°F to 46°F), and protect from light.  
243 Do not freeze or shake. Do not use ELAPRASE after the expiration date on the vial.

244 This product contains no preservatives. The diluted solution should be used immediately. If  
245 immediate use is not possible, the diluted solution can be stored refrigerated at 2°C to 8°C  
246 (36°F to 46°F) for up to 48 hours, or must be administered within 8 hours if held at room  
247 temperature.

## 248 **HOW SUPPLIED**

249 ELAPRASE is a sterile, aqueous, clear to slightly opalescent colorless solution supplied in a  
250 5 mL Type I glass vial. The vials are closed with a butyl rubber stopper with fluororesin coating  
251 and an aluminum overseal with a blue flip-off plastic cap.

252 NDC 54092-700-01

## 253 **Rx Only**

254 ELAPRASE is manufactured for:

255

256 Shire Human Genetic Therapies, Inc.

257 700 Main Street

258 Cambridge, MA 02139

259 US License Number XXXX

260 OnePath<sup>SM</sup> phone # 1-866-888-0660

261

262 ELAPRASE is a trademark of Shire Human Genetic Therapies, Inc.

263

264 **REV XX/DATE**

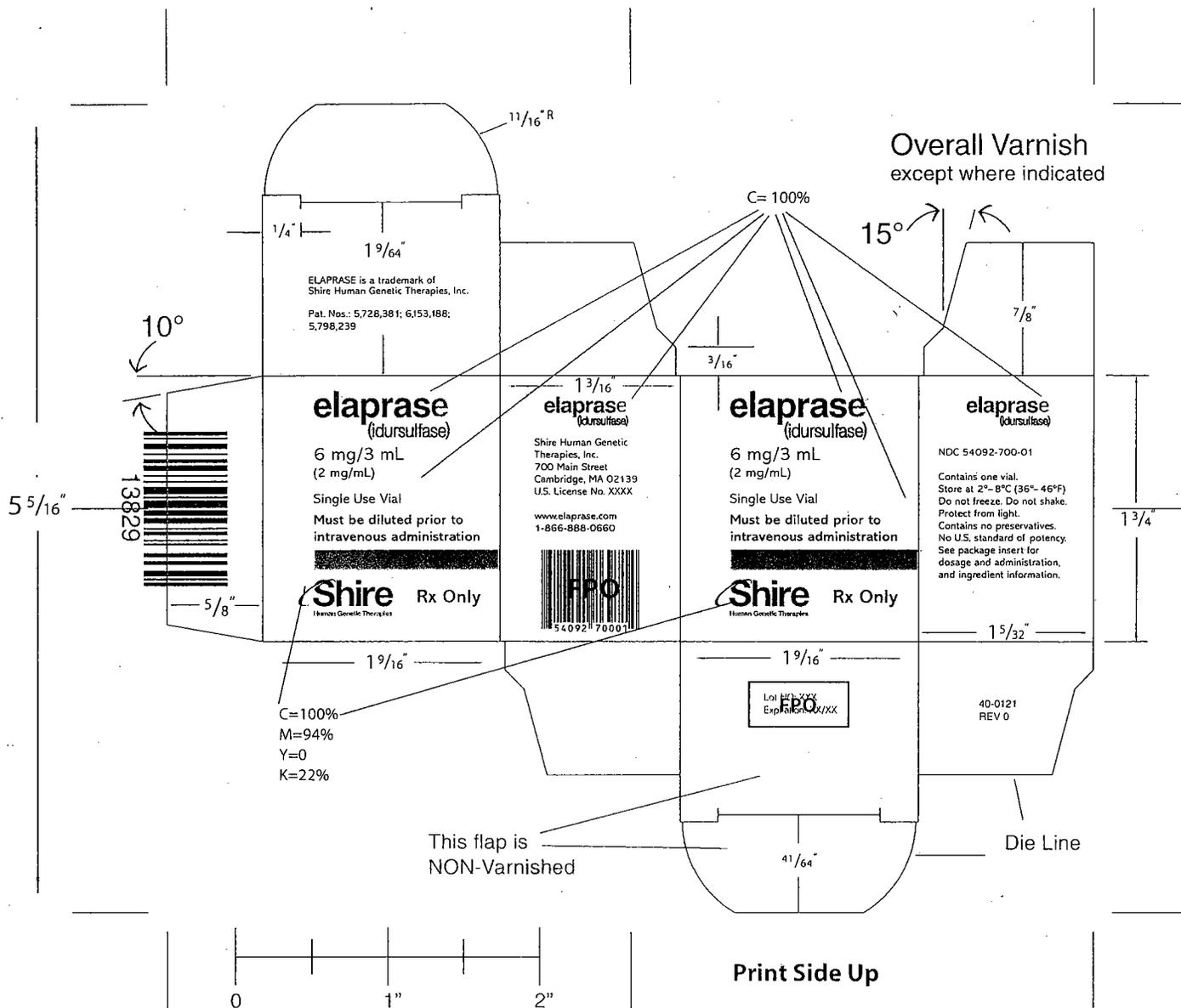
CLS

### 40-0121 Elaprase English Carton

BLACK, CYAN, PMS2748

DIE LINES IN MAGENTA

NOTE: All copy/art unmarked prints as Black



The above ruler represents 2 inches divided into half-inch segments at a scale of 100%.

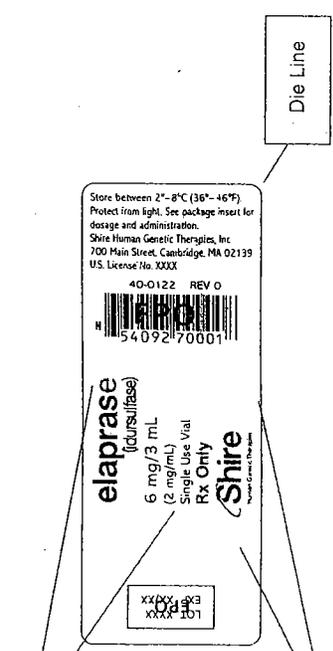
6 3/32"

C/S

### 40-0122 Elaprase US Vial Label

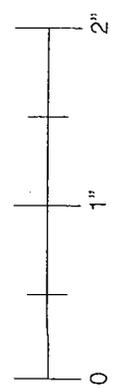
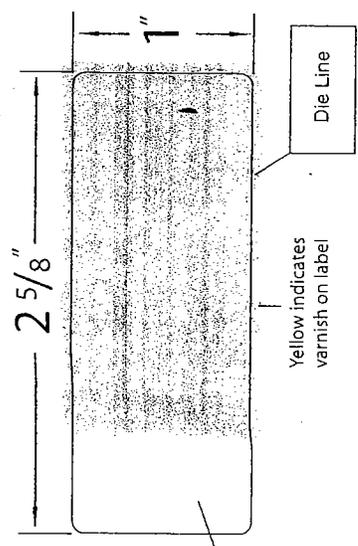
SHIRE HGT ITEM #: elaprase 40-0122  
BLACK, CYAN & PMS2748,

NOTE: All copy/art unmarked prints as Black



C= 100%

C=100%  
M=94%  
Y=0  
K=22%



The above ruler represents 2 inches divided into half-inch segments at a scale of 100%.