

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-479**

**PHARMACOLOGY REVIEW**

Barry N. Rosloff, Ph.D.  
2/6/03

**NDA 21-479 - SUPERVISORY MEMO TO FILE**

I concur with the recommendations made in Dr. Freed's excellent NDA review of 2/6/03.

(However, although I agree with the recommendation that a complete reproductive battery should be performed, I disagree with 1 of the 2 reasons given for this, i.e. that the Cmax for parent compound in humans is about 2x greater with this formulation compared to the marketed formulation. I do not think this is a large enough difference to warrant further testing. In addition, Cmax values for 3 major metabolites, which are present in significant quantities in humans, are significantly lower with the new formulation. In addition, human AUC values for both parent and metabolites are lower with the new formulation. [I agree with the second reason given, i.e. that there are no adequate reproduction studies to which the sponsor can refer]).

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## *Executive Summary*

### 1. Recommendations

#### 1.1 Recommendation on Approvability

From a pharmacology/toxicology standpoint, there is no objection to the approval of the NDA.

#### 1.2 Recommendation for Nonclinical Studies

It is recommended that the sponsor be asked to conduct a complete battery of reproductive and developmental toxicology and genotoxicity studies as a Phase 4 commitment (cf. *Guideline for Industry - Detection of Toxicity to Reproduction for Medicinal Products*; ICH-S5A, Sept 1994; *A Standard Battery for Genotoxicity Testing of Pharmaceuticals*; ICH-S2B, Jul 1997). The *in vivo* studies should be conducted using a route of administration that will result in plasma exposure to selegiline and major metabolites exceeding those expected in humans at the maximum recommended clinical dose.

#### 1.3 Recommendations on Labeling

The following labeling is recommended:

**CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY**

b(4)

b(5)

b(4)

b(5)

## 2. Summary of nonclinical Findings

The sponsor relied on the nonclinical database submitted to NDAs 19-334 (Eldepryl<sup>®</sup> tablet) and 20-647 (Eldepryl<sup>®</sup> capsule) to support the Zydis formulation of selegiline (Zelapar). In addition to those data, the sponsor conducted a 28-day toxicokinetic study in Beagle dog and a 4-wk cheek pouch study in Golden Syrian hamster. The 28-day TK study in dog provided an estimate of plasma drug exposure obtained in the 1-yr oral toxicity study submitted to NDA 19-334. The 4-wk cheek pouch study in hamster was conducted in order to assess the local effects of the Zelapar.

The human PK data indicated that total plasma exposure (i.e., AUC) for selegiline was slightly lower ( $\approx 20\%$  at 2.5 mg) with Zelapar compared to Eldepryl<sup>®</sup>, and total plasma exposures for metabolites (N-desmethylselegiline, l-amphetamine, l-methamphetamine) were markedly lower with Zelapar. Peak levels (i.e.,  $C_{max}$ ) of selegiline were  $\approx 2$ -fold higher with Zelapar compared to Eldepryl<sup>®</sup>. Based on the TK data collected in dog, it is estimated that peak plasma levels of selegiline achieved in the 1-yr study at the high-dose were slightly lower than that expected in humans at the maximum recommended clinical dose. However, the interindividual variability in plasma exposure was high in both dog and human, making interspecies comparisons difficult. In addition, drug-related effects in a transdermal toxicity study in dog were not clearly different from those observed in the 1-yr oral study, even though plasma levels were  $\approx 4$ -fold higher in the transdermal study. Therefore, the oral database in dog is probably sufficient to support approval of Zelapar.

No TK bridging data were provided for the other animal species (rat, rabbit, mouse) used in toxicity studies conducted to support NDAs 19-334 or 20-647. Considering the fairly similar plasma AUCs for selegiline obtained in humans with Zelapar and Eldepryl<sup>®</sup>, additional carcinogenicity test is not necessary. While a TK bridging study in rats would have been beneficial in estimating the plasma drug exposures achieved in the 1-yr oral toxicity study, the differences in plasma exposure between Zelapar and Eldepryl<sup>®</sup> in humans are probably not large enough to warrant additional general toxicology studies. However, the sponsor should be asked to conduct a complete reproductive and developmental toxicology battery as well as a complete battery of genotoxicity studies as a Phase 4 commitment. The need for reproductive studies is based on (a) a concern that peak plasma levels of selegiline are higher in humans with Zelapar compared to Eldepryl<sup>®</sup> and (b) the inadequacy of the reproductive

studies conducted in support of NDAs 19-334 and 20-647. The need for genotoxicity studies is based on the inadequacy of the genotoxicity studies conducted in support of NDAs 19-334 and 20-647.

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***PHARMACOLOGY/TOXICOLOGY REVIEW***

**I. PHARMACOLOGY**

Nonclinical pharmacology studies conducted under NDAs 19-334 (Eldepryl<sup>®</sup> tablets) and 20-647 (Eldepryl<sup>®</sup> capsules) were referenced in support of the NDA. No new nonclinical pharmacology studies were conducted.

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## II. SAFETY PHARMACOLOGY

Nonclinical pharmacology studies conducted under NDAs 19-334 (Eldepryl<sup>®</sup> tablets) and 20-647 (Eldepryl<sup>®</sup> capsules) were referenced in support of the NDA. No new safety pharmacology studies were conducted.

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**Results:**

Study 1: selected metabolite data from an acute-dose PK study submitted under the original NDA (19-334) were summarized in the table (provided by the sponsor, obtained from data included in the FDA NDA review for NDA 19-334) below. The AUC for N-desmethylselegiline was calculated based on data collected from 0 to 7 hrs postdosing; the AUCs for amphetamine and methamphetamine were based on data collected from 0 to 48 hrs postdosing.

**Table 1B: Original Values for Metabolite Concentrations: C<sub>max</sub>, t<sub>max</sub>, and AUC(t) at 3 mg/kg, Original Study**

| Dose Group |                               | N-Dseleg <sup>a</sup> | Amph <sup>b</sup> | Methamph <sup>c</sup> |
|------------|-------------------------------|-----------------------|-------------------|-----------------------|
| Original   | C <sub>max</sub> (ng/mL)      | 11.0                  | 102               | 87.4                  |
|            | t <sub>max</sub> (h)          | 0.67                  | 2.00              | 0.67                  |
|            | AUC(t) <sup>d</sup> (ng h/mL) | 9.76                  | 1685              | 416                   |

**(Note: according to the sponsor's summary table [as it appears in the FDA NDA review for NDA 19-334], the data for N-desmethylselegiline at 3 mg/kg were "defective". However, in the original study report, the AUC for the N-desmethylselegiline was 20 ng•hr/mL)**

The data from Study 1 were summarized in the following sponsor's tables:

**Table 2B: C<sub>max</sub>, t<sub>max</sub>, AUC(t), Mean, and SD for Selegiline Treated Beagle Dogs at 3 mg/kg, Fasted**

| Animal No. |                               | Seleg <sup>a</sup> | N-Dseleg <sup>b</sup> | Amph <sup>c</sup> | Methamph <sup>d</sup> |
|------------|-------------------------------|--------------------|-----------------------|-------------------|-----------------------|
| 3336492    | C <sub>max</sub> (ng/mL)      | 2.11               | 1.44                  | 173               | 130                   |
|            | t <sub>max</sub> (h)          | 4.00               | 0.67                  | 4.00              | 0.67                  |
|            | AUC(t) <sup>e</sup> (ng h/mL) | 17.4               | 3.62                  | 2048              | 300                   |
| 3336417    | C <sub>max</sub> (ng/mL)      | 2.56               | 2.24                  | 129               | 96.4                  |
|            | t <sub>max</sub> (h)          | 4.00               | 0.17                  | 4.00              | 0.67                  |
|            | AUC(t) <sup>e</sup> (ng h/mL) | 7.47               | 2.33                  | 1230              | 353                   |
| 3335852    | C <sub>max</sub> (ng/mL)      | 19.0               | 3.56                  | 115               | 97.1                  |
|            | t <sub>max</sub> (h)          | 0.17               | 0.17                  | 1.33              | 1.33                  |
|            | AUC(t) <sup>e</sup> (ng h/mL) | 20.7               | 5.13                  | 974               | 276                   |
| 3336026    | C <sub>max</sub> (ng/mL)      | 2.56               | 0.88                  | 145               | 105                   |
|            | t <sub>max</sub> (h)          | 4.00               | 0.67                  | 2.00              | 0.67                  |
|            | AUC(t) <sup>e</sup> (ng h/mL) | 6.47               | 0.99                  | 1174              | 313                   |
| Mean       | C <sub>max</sub> (ng/mL)      | 6.56               | 2.03                  | 141               | 107                   |
|            | t <sub>max</sub> (h)          | 3.04               | 0.42                  | 2.83              | 0.84                  |
|            | AUC(t) <sup>e</sup> (ng h/mL) | 13.0               | 3.02                  | 1357              | 310                   |
| SD         | C <sub>max</sub> (ng/mL)      | 8.30               | 1.16                  | 24.9              | 15.7                  |
|            | t <sub>max</sub> (h)          | 1.92               | 0.29                  | 1.38              | 0.33                  |
|            | AUC(t) <sup>e</sup> (ng h/mL) | 7.12               | 1.77                  | 474               | 32.2                  |

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**Table 3B: C<sub>max</sub>, t<sub>max</sub>, AUC(t), Mean, and SD for Selegiline Treated Beagle Dogs at 3 mg/kg, Fed**

| Animal No. |                               | Seleg <sup>a</sup> | N-Dseleg <sup>b</sup> | Amph <sup>c</sup> | Methamph <sup>d</sup> |
|------------|-------------------------------|--------------------|-----------------------|-------------------|-----------------------|
| 3336000    | C <sub>max</sub> (ng/mL)      | 69.0               | 5.74                  | 116               | 83.6                  |
|            | t <sub>max</sub> (h)          | 0.17               | 0.67                  | 2.00              | 1.33                  |
|            | AUC(t) <sup>e</sup> (ng h/mL) | 135                | 11.8                  | 1225              | 380                   |
| 3336115    | C <sub>max</sub> (ng/mL)      | 2.53               | 1.16                  | 157               | 82.2                  |
|            | t <sub>max</sub> (h)          | 0.17               | 0.67                  | 4.00              | 1.33                  |
|            | AUC(t) <sup>e</sup> (ng h/mL) | 5.87               | 1.53                  | 1655              | 312                   |
| 3336468    | C <sub>max</sub> (ng/mL)      | 1.33               | 0.49                  | 114               | 57.2                  |
|            | t <sub>max</sub> (h)          | 4.00               | 0.67                  | 4.00              | 1.33                  |
|            | AUC(t) <sup>e</sup> (ng h/mL) | 2.54               | 0.44                  | 1105              | 175                   |
| 3337812    | C <sub>max</sub> (ng/mL)      | 53.5               | 4.23                  | 122               | 35.8                  |
|            | t <sub>max</sub> (h)          | 0.17               | 0.17                  | 4.00              | 1.33                  |
|            | AUC(t) <sup>e</sup> (ng h/mL) | 51.5               | 4.71                  | 1127              | 201                   |
| Mean       | C <sub>max</sub> (ng/mL)      | 31.6               | 2.91                  | 127               | 64.7                  |
|            | t <sub>max</sub> (h)          | 1.13               | 0.55                  | 3.50              | 1.33                  |
|            | AUC(t) <sup>e</sup> (ng h/mL) | 48.8               | 4.61                  | 1278              | 267                   |
| SD         | C <sub>max</sub> (ng/mL)      | 34.8               | 2.49                  | 20.1              | 22.8                  |
|            | t <sub>max</sub> (h)          | 1.92               | 0.25                  | 1.00              | 0.00                  |
|            | AUC(t) <sup>e</sup> (ng h/mL) | 61.7               | 5.09                  | 257               | 96.2                  |

The sponsor noted that the AUC and C<sub>max</sub> data for N-desmethylselegiline from the original PK study were "questionable because they appear to have been generated from only one dog out of the 4 dosed" and that the plasma levels were close to the LLOD. The sponsor concluded that since the plasma amphetamine data in fasted dogs were the most similar to the original data, and considering that amphetamine is the major metabolite, the 28-day study should be conducted in fasted dogs.

Study 2: summary tables were not provided for the data (only individual line listings were given). Drug-related clinical signs were evident primarily at the HD. The data are summarized in the following table:

| SIGN                      | MALES |     |     | FEMALES |     |     |
|---------------------------|-------|-----|-----|---------|-----|-----|
|                           | LD    | MD  | HD  | LD      | MD  | HD  |
| hyperactivity             | 0/2   | 0/2 | 2/2 | 0/2     | 0/2 | 1/2 |
| salivation                | 0/2   | 0/2 | 1/2 | 0/2     | 0/2 | 2/2 |
| mydriasis                 | 0/2   | 0/2 | 2/2 | 0/2     | 0/2 | 2/2 |
| ocular scleral erythema   | 0/2   | 1/2 | 1/2 | 0/2     | 0/2 | 2/2 |
| white residue around anus | 0/2   | 1/2 | 1/2 | 0/2     | 0/2 | 2/2 |
| thin                      | 0/2   | 1/2 | 2/2 | 0/2     | 0/2 | 1/2 |

The sponsor noted that the severity of clinical signs at the HD were mild-to-moderate. Hyperactivity was primarily observed during Wks 3-4; salivation was noted periodically throughout the dosing period.

Body wt loss was observed at all doses; however, only 1 animal was affected at the LD (1 F). Mean body wt loss was observed at the MD and HD (≈ -0.4 and -0.8 kg, respectively); mean



Table 2: C<sub>max</sub> (ng/mL) for Selegiline and Metabolites in Beagle Dogs after 28 Oral Doses of Selegiline HCl

| Dose     | Dog #   | Sex  | Seleg <sup>a</sup> |        | N-desleg <sup>b</sup> |        | Amph <sup>c</sup> |        | Methamph <sup>d</sup> |        |
|----------|---------|------|--------------------|--------|-----------------------|--------|-------------------|--------|-----------------------|--------|
|          |         |      | Day 0              | Day 27 | Day 0                 | Day 27 | Day 0             | Day 27 | Day 0                 | Day 27 |
| 1 mg/kg  | 3290824 | M    | 0.66               | 0.61   | 2.18                  | 0.46   | 60.2              | 50.3   | 76.4                  | 35.1   |
|          | 3293629 | M    | 0.69               | 0.60   | 0.00                  | 0.00   | 58.8              | 60.0   | 23.4                  | 31.9   |
|          | 3301044 | F    | 1.10               | 0.00   | 0.00                  | 0.00   | 51.0              | 64.0   | 24.7                  | 26.7   |
|          | 3302229 | F    | 0.49               | 3.70   | 0.00                  | 1.24   | 51.4              | 58.0   | 24.4                  | 34.4   |
|          |         | Mean | 0.73               | 1.23   | 0.55                  | 0.42   | 55.4              | 58.1   | 37.2                  | 32.0   |
|          |         | SD   | 0.26               | 1.67   | 1.09                  | 0.58   | 4.83              | 5.75   | 26.1                  | 3.81   |
| 4 mg/kg  | 3291243 | M    | 7.92               | 81.0   | 2.53                  | 9.93   | 184               | 197    | 115                   | 45.1   |
|          | 3298477 | F    | 2.72               | 24.1   | 9.35                  | 11.4   | 143               | 176    | 186                   | 186    |
|          | 3301290 | F    | 4.20               | 4.11   | 1.87                  | 2.84   | 187               | 201    | 117                   | 178    |
|          | 3302318 | M    | 2.79               | 1.27   | 1.34                  | 1.26   | 177               | 221    | 129                   | 146    |
|          |         | Mean | 4.41               | 27.6   | 3.77                  | 6.36   | 173               | 199    | 137                   | 139    |
|          |         | SD   | 2.44               | 37.0   | 3.75                  | 5.05   | 20.3              | 18.4   | 33.4                  | 64.8   |
| 16 mg/kg | 3300668 | F    | 33.8               | 6.69   | 41.6                  | 28.3   | 539               | 671    | 563                   | 563    |
|          | 3301354 | F    | 564                | 574    | 634                   | 153    | 933               | 723    | 1387                  | 984    |
|          | 3303021 | M    | 16.1               | 8.16   | 33.1                  | 22.5   | 429               | 714    | 339                   | 528    |
|          | 3303055 | M    | 19.5               | 10.5   | 49.9                  | 53.3   | 341               | 706    | 439                   | 913    |
|          |         | Mean | 158                | 150    | 190                   | 64.3   | 561               | 704    | 707                   | 797    |
|          |         | SD   | 271                | 283    | 296                   | 60.6   | 261               | 22.8   | 473                   | 178    |

Table 3: AUC<sub>(0-24)</sub> (ng.h/mL) for Selegiline and Metabolites in Beagle Dogs after 28 Oral Doses of Selegiline HCl

| Dose     | Dog #   | Sex  | Seleg <sup>a</sup> |        | N-desleg <sup>b</sup> |        | Amph <sup>c</sup> |        | Methamph <sup>d</sup> |        |
|----------|---------|------|--------------------|--------|-----------------------|--------|-------------------|--------|-----------------------|--------|
|          |         |      | Day 0              | Day 27 | Day 0                 | Day 27 | Day 0             | Day 27 | Day 0                 | Day 27 |
| 1 mg/kg  | 3290824 | M    | 1.32               | 2.93   | 0.56                  | 0.11   | 605               | 656    | 121                   | 106    |
|          | 3293629 | M    | 2.42               | 2.26   | 0.00                  | 0.00   | 572               | 633    | 93.5                  | 90.6   |
|          | 3301044 | F    | 3.84               | 0.00   | 0.00                  | 0.00   | 414               | 565    | 79.5                  | 58.7   |
|          | 3302229 | F    | 0.49               | 2.17   | 0.00                  | 0.90   | 514               | 484    | 77.7                  | 56.4   |
|          |         | Mean | 2.02               | 1.84   | 0.14                  | 0.25   | 526               | 584    | 92.9                  | 77.9   |
|          |         | SD   | 1.45               | 1.27   | 0.28                  | 0.43   | 83.7              | 77.5   | 20.0                  | 24.3   |
| 4 mg/kg  | 3291243 | M    | 43.9               | 125    | 8.75                  | 22.7   | 1903              | 1959   | 392                   | 412    |
|          | 3298477 | F    | 11.6               | 28.5   | 8.80                  | 12.0   | 1507              | 2006   | 399                   | 445    |
|          | 3301290 | F    | 36.0               | 17.9   | 4.00                  | 3.42   | 1954              | 1948   | 372                   | 461    |
|          | 3302318 | M    | 13.4               | 6.18   | 3.73                  | 0.68   | 1689              | 2092   | 369                   | 382    |
|          |         | Mean | 26.2               | 44.4   | 6.32                  | 9.71   | 1763              | 2001   | 383                   | 425    |
|          |         | SD   | 16.2               | 54.6   | 2.84                  | 9.92   | 206               | 65.35  | 14.7                  | 34.9   |
| 16 mg/kg | 3300668 | F    | 112                | 39.2   | 59.1                  | 50.9   | 5891              | 7497   | 3395                  | 3208   |
|          | 3301354 | F    | 345                | 459    | 399                   | 172    | 13606             | 7916   | 5983                  | 2945   |
|          | 3303021 | M    | 115                | 52.2   | 101                   | 53.3   | 7055              | 7785   | 2391                  | 2968   |
|          | 3303055 | M    | 132                | 52.2   | 133                   | 94.2   | 6028              | 9497   | 2742                  | 4624   |
|          |         | Mean | 176                | 151    | 173                   | 92.6   | 8145              | 8174   | 3628                  | 3436   |
|          |         | SD   | 113                | 206    | 154                   | 56.5   | 3677              | 899    | 1624                  | 801    |

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Table 4: Terminal Half-Life (h) of Selegiline and Metabolites in Beagle Dogs after 28 Oral Doses of Selegiline HCl

| Dose     | Dog #   | Sex  | Seleg <sup>a</sup> |        | N-desleg <sup>b</sup> |        | Amph <sup>c</sup> |        | Methamph <sup>d</sup> |        |
|----------|---------|------|--------------------|--------|-----------------------|--------|-------------------|--------|-----------------------|--------|
|          |         |      | Day 0              | Day 27 | Day 0                 | Day 27 | Day 0             | Day 27 | Day 0                 | Day 27 |
| 1 mg/kg  | 3290824 | M    | uc <sup>e</sup>    | 0.73   | 0.07                  | uc     | 6.64              | 7.49   | 2.15                  | 2.21   |
|          | 3293629 | M    | 0.72               | 0.73   | uc                    | uc     | 6.11              | 6.99   | 1.87                  | 2.03   |
|          | 3301044 | F    | 0.69               | uc     | uc                    | uc     | 3.31              | 6.82   | 0.62                  | 0.70   |
|          | 3302229 | F    | uc                 | 0.33   | uc                    | 0.15   | 5.56              | 7.08   | 2.11                  | 0.71   |
|          |         | Mean | 0.71               | 0.60   | 0.07                  | 0.15   | 5.41              | 7.10   | 1.69                  | 1.41   |
|          |         | SD   | 0.02               | 0.23   | uc                    | uc     | 1.46              | 0.28   | 0.72                  | 0.82   |
| 4 mg/kg  | 3291243 | M    | 2.20               | 1.51   | 0.79                  | 0.79   | 7.25              | 13.35  | 2.29                  | 3.03   |
|          | 3298477 | F    | 0.61               | 0.74   | 0.42                  | 0.41   | 5.25              | 13.25  | 1.87                  | 3.46   |
|          | 3301290 | F    | 3.56               | 0.73   | 0.52                  | 0.28   | 5.18              | 12.97  | 1.77                  | 3.06   |
|          | 3302318 | M    | 0.62               | 0.53   | 0.36                  | 0.16   | 4.75              | 13.34  | 1.74                  | 3.14   |
|          |         | Mean | 1.75               | 0.88   | 0.52                  | 0.41   | 5.61              | 13.23  | 1.92                  | 3.17   |
|          |         | SD   | 1.42               | 0.43   | 0.19                  | 0.27   | 1.12              | 0.18   | 0.25                  | 0.20   |
| 16 mg/kg | 3300668 | F    | 4.16               | 1.63   | 0.71                  | 0.69   | 4.48              | 11.83  | 2.02                  | 18.00  |
|          | 3301354 | F    | 6.00               | 2.87   | 2.03                  | 2.28   | 9.07              | 12.55  | 2.28                  | 13.81  |
|          | 3303021 | M    | 2.11               | 1.57   | 1.85                  | 0.64   | 16.03             | 11.57  | 3.54                  | 12.89  |
|          | 3303055 | M    | 4.61               | 1.56   | 1.62                  | 0.60   | 19.01             | 10.21  | 2.66                  | 10.51  |
|          |         | Mean | 4.22               | 1.91   | 1.55                  | 1.05   | 12.15             | 11.54  | 2.63                  | 13.80  |
|          |         | SD   | 1.61               | 0.64   | 0.59                  | 0.82   | 6.59              | 0.98   | 0.66                  | 3.12   |

Based on these data, the sponsor concluded that "...there was systemic exposure to selegiline in dogs following oral administration of selegiline HCl".

The sponsor provided copies of two published studies:

(1) Barrett JS *et al.* Toxicokinetic evaluation of a selegiline transdermal system in the dog. *Biopharm Drug Disp* 18(2):165-184, 1997.

This article provided TK data from a 3-mo study in Beagle dogs. Selegiline was administered as a transdermal patch (STS) at doses of 0, 4, 8, and 12 STSs (each STS contained ≈5 mg of selegiline). Patches were replaced daily. Estimated delivered doses were 2.89, 5.84, and 8.54 mg/kg/day at the LD, MD, and HD, respectively. Steady-state plasma levels were summarized in the following table (obtained directly from the published article) (the AUC data were calculated over 37- and 96-day periods):

Table 6. Mean selegiline and metabolite steady-state plasma concentrations (ng mL<sup>-1</sup>) following daily 24 h applications of 4, 8, or 12 STSs for 13 weeks

|         | C <sub>ss</sub> (ng mL <sup>-1</sup> ) |                       |               |                   |
|---------|--|-----------------------|---------------|-------------------|
|         | Selegiline                             | N-desmethylselegiline | L-amphetamine | L-methamphetamine |
| 4 STSs  | 12.3 ± 4.8                             | 2.2 ± 1.1             | 50.8 ± 16.5   | 9.3 ± 3.5         |
| 8 STSs  | 30.2 ± 11.3                            | 2.9 ± 1.2             | 85.1 ± 26.3   | 16.0 ± 7.0        |
| 12 STSs | 41.1 ± 20.8                            | 4.2 ± 2.2             | 126.1 ± 54.3  | 28.5 ± 14.8       |

The authors noted that "There were no test-material-related observations" on various parameters assessed (including clinical signs, dermal irritation, ECG, clinical pathology, ophthalmology). It was noted that "mild" increases in ALT and deposition of pigment in Kupffer cells in liver were observed at the MD and HD.

(2) Seager H. Drug-delivery products and the Zydis fast-dissolving dosage form. *J Pharm Pharmacol* 50:375-382, 1997.

This article primarily described the "formulation and process technology of the Zydis dosage form". However, there was some discussion of the absorption of selegiline from Zydis and conventional oral dosage forms. Seager (1997) noted that selegiline is an example of a drug that, in the Zydis form, dissolves in saliva and is "...absorbed into the bloodstream through the membranes of the mouth, pharynx and oesophagus during the swallowing process". The absolute bioavailability of Zydis selegiline is, therefore, increased since pre-gastric absorption avoids first-pass metabolism. Therefore, lower doses of selegiline may be used and lower systemic exposure to metabolites may result.

Mean AUCs for selegiline, N-desmethylselegiline, methamphetamine, and amphetamine following Zydis and "Movergan" oral tablets were reported as follows:

Zydis (1.25 mg): 2.8, 9.5, 114.2, and 56.4 nM h, respectively.  
oral tablet (10 mg): 2.0, 203.3, 1521.0, and 698.7 nM h, respectively.

#### Human PK/ADME

The human PK/ADME data were reviewed only to the extent necessary to document the comparison between the PK/ADME of selegiline following convention oral dosing (tablet/capsule) at the recommended dose (5 mg b.i.d.) and that following administration of the Zydis formulation. The following information was provided in the sponsor's summary. Additional human PK data are discussed in the PK/TK Summary and Conclusion section.

PK data were not collected in PD patients. Data from two studies (Z/SEL/97/035, Z/SEL/97/026) indicated that trough levels of selegiline were 0.246 ng/mL (1.25 mg/day, Wk 4) and 0.8380 ng/mL (2.5 mg/day, Wk 12). Plasma levels were <LLOQ by 4 and 12 hrs postdosing for the 1.25- and 2.5-mg doses, respectively.

PK data were collected in 9 studies conducted in healthy age-matched volunteers at doses of 1.25-10 mg of the Zydis formulation. In each study, subjects were instructed to "...place the tablet on the tongue, allowing it to dissolve, holding the dissolved material in the mouth for 1-2 minutes, then swallowing normally". According to the sponsor's summary, "...only Study AN17933-101 evaluated a full range of relevant doses for Zydis selegiline (1.25, 2.5, and 5.0 mg for single doses and at steady state) and compared them to Eldepryl administered in a manner consistent with the approved labeling (given as two 5.0 mg tablets four hours apart)." The bioavailability of selegiline from the Zydis and tablet formulations was assessed in Study 001.

Study Z/SEL/95/001: Zydis selegiline (1.25 mg) and Eldepryl (10 mg) were administered to 10 healthy volunteers. Selegiline, N-demethylselegiline, L-methamphetamine, and L-amphetamine

were quantitated in urine samples collected up to 96 hrs postdosing. Urinary concentrations of selegiline and metabolites accounted for ≈33 and 44% of dose following Zydys selegiline and Eldepryl, respectively. In plasma, peak drug (nos) levels were achieved by 15 min postdosing.

Study AN17933-101: Zydys selegiline (1.25, 2.5, and 5 mg) and Eldepryl (5 mg b.i.d.) were administered to healthy volunteers. Data from Study AN17933-101 were summarized in the following sponsor's tables:

**Table 3.6-2: Mean (SD)<sup>a</sup> Day 1 and Day 10  
Selegiline Pharmacokinetic Parameters—Study AN17933-101**

| Treatment   | Day 1                       |                         |                               | Day 10                         |                                |                            |                               |
|---|-----------------------------|-------------------------|-------------------------------|--------------------------------|--------------------------------|----------------------------|-------------------------------|
|   | C <sub>max</sub><br>(ng/mL) | t <sub>max</sub><br>(h) | AUC <sub>t</sub><br>(ng·h/mL) | C <sub>ss,max</sub><br>(ng/mL) | C <sub>ss,min</sub><br>(ng/mL) | t <sub>ss,max</sub><br>(h) | AUC <sub>t</sub><br>(ng·h/mL) |
| Zydys Selegiline<br>1.25 mg OD<br>(N = 15)              | 3.34<br>(1.68)              | 0.17<br>(0.17–0.27)     | 1.49<br>(0.77)                | 3.96<br>(1.90)                 | 0.03<br>(0.03)                 | 0.25<br>(0.17–0.50)        | 4.77<br>(2.29)                |
| Zydys Selegiline<br>2.5 mg OD<br>(N = 16 <sup>b</sup> ) | 4.47<br>(2.56)              | 0.18<br>(0.08–0.50)     | 2.44<br>(1.64)                | 4.37<br>(1.83)                 | 0.05<br>(0.04)                 | 0.25<br>(0.17–0.50)        | 6.52<br>(2.09)                |
| Zydys Selegiline<br>5.0 mg OD<br>(N = 15 <sup>c</sup> ) | 5.45<br>(3.24)              | 0.18<br>(0.10–0.50)     | 3.78<br>(2.03)                | 5.54<br>(3.01)                 | 0.06<br>(0.04)                 | 0.25<br>(0.17–0.78)        | 8.51<br>(2.74)                |
| Eldepryl <sup>®</sup><br>5.0 mg BID<br>(N = 17)         | 1.12<br>(1.48)              | 4.55<br>(0.50–6.03)     | 1.93<br>(1.67)                | 1.73<br>(1.08)                 | 0.09<br>(0.07)                 | 1.00<br>(0.25–6.00)        | 8.32<br>(5.06)                |

<sup>a</sup> Median (range) for t<sub>max</sub> and t<sub>ss,max</sub>.

<sup>b</sup> N = 15 for Day 10, Subject 35 withdrew on Day 9.

<sup>c</sup> N = 14 for Day 10, Subject 46 withdrew on Day 9.

**Table 3.6-4: Mean (SD)<sup>a</sup> Day 1 and Day 10  
L-amphetamine Pharmacokinetic Parameters—Study AN17933-101**

| Treatment   | Day 1                       |                         |                               | Day 10                         |                                |                            |                               |
|---|-----------------------------|-------------------------|-------------------------------|--------------------------------|--------------------------------|----------------------------|-------------------------------|
|   | C <sub>max</sub><br>(ng/mL) | t <sub>max</sub><br>(h) | AUC <sub>t</sub><br>(ng·h/mL) | C <sub>ss,max</sub><br>(ng/mL) | C <sub>ss,min</sub><br>(ng/mL) | t <sub>ss,max</sub><br>(h) | AUC <sub>t</sub><br>(ng·h/mL) |
| Zydys Selegiline<br>1.25 mg OD<br>(N = 15)              | 0.20<br>(0.09)              | 1.80<br>(1.00–6.02)     | 1.49<br>(1.54)                | 1.19<br>(1.68)                 | 0.28<br>(0.09)                 | 3.00<br>(1.00–12.13)       | 11.92<br>(5.13)               |
| Zydys Selegiline<br>2.5 mg OD<br>(N = 16 <sup>b</sup> ) | 0.58<br>(0.15)              | 4.00<br>(0.75–12.00)    | 8.00<br>(1.48)                | 1.78<br>(0.82)                 | 0.60<br>(0.26)                 | 3.00<br>(1.00–6.00)        | 26.92<br>(7.92)               |
| Zydys Selegiline<br>5.0 mg OD<br>(N = 15 <sup>c</sup> ) | 1.33<br>(0.28)              | 3.00<br>(1.00–6.00)     | 19.94<br>(3.78)               | 3.24<br>(0.60)                 | 1.14<br>(0.39)                 | 3.00<br>(0.92–6.00)        | 50.63<br>(10.42)              |
| Eldepryl <sup>®</sup><br>5.0 mg BID<br>(N = 17)         | 2.69<br>(0.65)              | 8.00<br>(4.50–23.93)    | 44.17<br>(8.28)               | 5.30<br>(1.07)                 | 2.62<br>(0.59)                 | 8.00<br>(0.50–12.00)       | 95.25<br>(16.90)              |

<sup>a</sup> Median (range) for t<sub>max</sub> and t<sub>ss,max</sub>.

<sup>b</sup> N = 15 for Day 10, Subject 35 withdrew on Day 9.

<sup>c</sup> N = 14 for Day 10, Subject 46 withdrew on Day 9.

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**Table 3.6-3: Mean (SD)<sup>a</sup> Day 1 and Day 10**  
**N-desmethylselegiline Pharmacokinetic Parameters—Study AN17933-101**

| Treatment   | Day 1                       |                         |                               | Day 10                         |                                |                            |                               |
|---|-----------------------------|-------------------------|-------------------------------|--------------------------------|--------------------------------|----------------------------|-------------------------------|
|   | C <sub>max</sub><br>(ng/mL) | t <sub>max</sub><br>(h) | AUC <sub>t</sub><br>(ng-h/mL) | C <sub>ss,max</sub><br>(ng/mL) | C <sub>ss,min</sub><br>(ng/mL) | t <sub>ss,max</sub><br>(h) | AUC <sub>t</sub><br>(ng-h/mL) |
| Zydis Selegiline<br>1.25 mg OD<br>(N = 15)              | 1.22<br>(0.48)              | 1.00<br>(0.75–1.50)     | 2.07<br>(0.71)                | 2.06<br>(0.69)                 | 0.04<br>(0.05)                 | 1.00<br>(0.75–2.00)        | 8.66<br>(4.39)                |
| Zydis Selegiline<br>2.5 mg OD<br>(N = 16 <sup>b</sup> ) | 4.02<br>(2.05)              | 1.00<br>(0.75–3.00)     | 8.03<br>(3.64)                | 6.07<br>(3.39)                 | 0.16<br>(0.09)                 | 1.00<br>(0.50–1.52)        | 22.13<br>(10.09)              |
| Zydis Selegiline<br>5.0 mg OD<br>(N = 15 <sup>c</sup> ) | 7.36<br>(3.16)              | 1.00<br>(0.50–2.00)     | 17.14<br>(5.16)               | 10.10<br>(4.24)                | 0.19<br>(0.12)                 | 1.00<br>(0.50–3.00)        | 32.29<br>(10.28)              |
| Eldepryl <sup>®</sup><br>5.0 mg BID<br>(N = 17)         | 10.65<br>(5.09)             | 1.50<br>(0.50–8.00)     | 64.03<br>(38.56)              | 14.56<br>(6.44)                | 1.00<br>(0.85)                 | 1.50<br>(0.25–6.17)        | 100.96<br>(56.22)             |

<sup>a</sup> Median (range) for t<sub>max</sub> and t<sub>ss,max</sub>.  
<sup>b</sup> N = 15 for Day 10, Subject 35 withdrew on Day 9.  
<sup>c</sup> N = 14 for Day 10, Subject 46 withdrew on Day 9

**Table 3.6-5: Mean (SD)<sup>a</sup> Day 1 and Day 10**  
**L-methamphetamine Pharmacokinetic Parameters—Study AN17933-101**

| Treatment   | Day 1                       |                         |                               | Day 10                         |                                |                            |                               |
|---|-----------------------------|-------------------------|-------------------------------|--------------------------------|--------------------------------|----------------------------|-------------------------------|
|   | C <sub>max</sub><br>(ng/mL) | t <sub>max</sub><br>(h) | AUC <sub>t</sub><br>(ng-h/mL) | C <sub>ss,max</sub><br>(ng/mL) | C <sub>ss,min</sub><br>(ng/mL) | t <sub>ss,max</sub><br>(h) | AUC <sub>t</sub><br>(ng-h/mL) |
| Zydis Selegiline<br>1.25 mg OD<br>(N = 15)              | 0.62<br>(0.23)              | 1.50<br>(1.00–3.00)     | 5.68<br>(2.44)                | 1.78<br>(0.84)                 | 0.51<br>(0.21)                 | 2.00<br>(1.00–12.13)       | 24.45<br>(11.79)              |
| Zydis Selegiline<br>2.5 mg OD<br>(N = 16 <sup>b</sup> ) | 1.86<br>(0.49)              | 1.50<br>(0.75–4.00)     | 20.17<br>(4.27)               | 4.29<br>(1.63)                 | 0.93<br>(0.50)                 | 2.02<br>(0.75–6.00)        | 53.88<br>(15.56)              |
| Zydis Selegiline<br>5.0 mg OD<br>(N = 15 <sup>c</sup> ) | 5.00<br>(1.53)              | 1.50<br>(1.00–4.02)     | 57.49<br>(12.63)              | 8.76<br>(1.51)                 | 2.17<br>(0.85)                 | 1.26<br>(0.50–6.12)        | 113.76<br>(36.91)             |
| Eldepryl <sup>®</sup><br>5.0 mg BID<br>(N = 17)         | 8.37<br>(1.28)              | 8.00<br>(5.00–12.53)    | 131.34<br>(21.83)             | 16.23<br>(2.72)                | 5.12<br>(1.55)                 | 6.00<br>(1.50–12.00)       | 254.98<br>(66.55)             |

<sup>a</sup> Median (range) for t<sub>max</sub> and t<sub>ss,max</sub>.  
<sup>b</sup> N = 15 for Day 10, Subject 35 withdrew on Day 9.  
<sup>c</sup> N = 14 for Day 10, Subject 46 withdrew on Day 9.

**PK/TK summary and conclusions**

According to the sponsor, the initial impetus for developing a Zydis formulation of selegiline was to provide an oral dosage form that would be easier for PD patients to swallow, "...particularly those patients experiencing swallowing pain or dysphagia". Improvement in the ease of administration was thought to result in greater compliance in these patients.

The sponsor of IND 47,005 [Scherer DDS, Zydis selegiline] originally stated that the 1.25 tablet of Zydis selegiline would result in plasma selegiline levels similar to those following the 10-mg oral dose of conventional selegiline. However, data from initial bioequivalence studies "...revealed that selegiline exhibited a significantly different pharmacokinetic profile as the Zydis dosage form than as standard tablet formulations". This unexpected result was due to the absorption of selegiline through the buccal mucosa, thus, bypassing first-pass metabolism. As a

result, higher plasma levels of selegiline and lower plasma levels of metabolites were observed following the Zydys formulation than after the tablet/capsule.

Several critical questions need to be addressed in order to evaluate the adequacy of the nonclinical oral database to support the Zydys formulation: (a) is the metabolic profile of selegiline comparable with the Zydys and the tablet/capsule formulations, (b) how does the plasma exposure for selegiline and metabolites obtained with the Zydys formulation compare to that with the tablet in humans at the maximum recommended dose, and (c) if the plasma exposure is greater with the Zydys formulation, are there sufficient data to document adequate exposure in the nonclinical oral database. If the metabolic profile is comparable with the two formulations, and the plasma levels of selegiline (and metabolites) with the Zydys formulation at the maximum recommended clinical dose (i.e., 2.5 mg qd) do not exceed (to any notable extent) those obtained with the Eldepryl<sup>®</sup> tablet at the recommended clinical dose (i.e., 5 mg b.i.d.), then no further consideration of plasma exposures in animals would be necessary.

According to the Clinical Pharmacology/Biopharmaceutics Review (Veneeta Tandon, Ph.D.), the PK of Zydys selegiline (1.25 mg) and Eldepryl<sup>®</sup> tablets (10 mg) were compared in 4 clinical trials (Studies Z/SEL/95/023, Z/SEL/95/003, Z/SEL/96/014, and AN17933-101). The characteristics of these studies (based on information provided in the CP/B review [Veneeta Tandon, Ph.D.]) are summarized in the following table:

|              |  |
|--------------|--|
| Z/SEL/95/023 | acute dose, crossover, Eldepryl <sup>®</sup> U.S. product*   |
| Z/SEL/95/003 | acute dose, incomplete crossover (each subject received 2 of 4 treatments), Eldepryl <sup>®</sup> U.K. product |
| Z/SEL/96/014 | multiple dose, parallel group, Eldepryl <sup>®</sup> U.K. product  |
| AN17933-101  | multiple dose, parallel group, Eldepryl <sup>®</sup> U.S. product  |

\* the sponsor did not provide information on how the U.S. product compares to the U.K. product. Eldepryl<sup>®</sup> was administered b.i.d. only in Study AN17933-101

(One other study [Z/SEL/95/007] assessed the PK of Zydys selegiline and Eldepryl in humans following multiple dosing. However, since that study only used a 10-mg dose of Zydys, the data were not considered in this review.)

It was the sponsor opinion that Study AN17933-101 provided the most appropriate data since (a) "...a full range of relevant doses..." of Zydys selegiline was tested after acute and multiple dosing and that (b) Eldepryl was "...administered in a manner consistent with the approved labeling..." However, since there were notable differences in exposure among the 4 clinical trials (data provided below), it was difficult to determine which of the studies provided the "best" data for determining differences in exposure between the Zydys and tablet formulations or for basing interspecies comparisons.

The acute-dose data for selegiline from the 4 clinical trials are summarized in the following tables (the data for the 1.25-mg dose were obtained from the CP/B review):

| FORMULATION                           | DOSE (mg) | STUDY NO.    |              |              |             |
|---------------------------------------|-----------|--------------|--------------|--------------|-------------|
|                                       |           | Z/SEL/95/023 | Z/SEL/95/003 | Z/SEL/96/014 | AN17933-101 |
| <b>C<sub>max</sub> (ng/mL)</b>        |           |              |              |              |             |
| Zydis                                 | 1.25      | 1.12         | 2.36         | 1.44         | 3.34        |
|                                       | 2.5       |              | 3.38         |              | 4.47        |
| Eldepryl® U.S.                        | 5 x 2*    | 0.456        |              |              | 1.12        |
| Eldepryl® U.K.                        |           |              | 1.50         | 1.29         |             |
| <b>AUC<sub>(0-∞)</sub> (ng•hr/mL)</b> |           |              |              |              |             |
| Zydis                                 | 1.25      | 0.525        | 1.31         | 0.70         | 1.49        |
|                                       | 2.5       |              | 2.29         |              | 2.44        |
| Eldepryl® U.S.                        | 5 x 2*    | 0.37         |              |              | 1.93        |
| Eldepryl® U.K.                        |           |              | 1.42         | 1.09         |             |

\*Eldepryl® was administered b.i.d. only in Study AN17933-101

Acute and steady-state data from Studies Z/SEL/95/014 and AN17933-101 are provided in the following table (the data were obtained from the CP/B review):

| STUDY | FORMULATION    | DOSE (mg) | ACUTE                    |                                 | MULTIPLE-DOSE <sup>#</sup> |                                 |
|-------|----------------|-----------|--------------------------|---------------------------------|----------------------------|---------------------------------|
|       |                |           | C <sub>max</sub> (ng/mL) | AUC <sub>(0-∞)</sub> (ng•hr/mL) | C <sub>max</sub> (ng/mL)   | AUC <sub>(0-∞)</sub> (ng•hr/mL) |
| 014   | Zydis          | 1.25      | 1.44                     | 0.7                             | 3.38                       | 6.39                            |
|       | Eldepryl® U.K. | 5 x 2     | 1.29                     | 1.09                            | 4.15                       | 11.41                           |
| 101   | Zydis          | 1.25      | 3.34                     | 1.49                            | 3.96                       | 4.77                            |
|       |                | 2.5       | 4.47                     | 2.44                            | 4.37                       | 6.52                            |
|       | Eldepryl® U.S. | 5 x 2     | 1.12                     | 1.93                            | 1.73                       | 8.32                            |

\*Eldepryl® was administered b.i.d. only in Study AN17933-101; <sup>#</sup>Day 28 for Z/SEL/95/014, Day 10 for AN17933-101

Plasma exposure ratios following acute and repeated dosing are compared in the following table:

| FORMULATION            | DOSE (mg) | Z/SEL/96/014 (Day 28/Day 1) | AN17933-101 (Day 10/Day 1) |
|------------------------|-----------|-----------------------------|----------------------------|
| <b>C<sub>max</sub></b> |           |                             |                            |
| Zydis                  | 1.25      | 2.3                         | 1.2                        |
|                        | 2.5       |                             | 1                          |
| Eldepryl® U.S.         | 5 x 2     |                             | 1.5                        |
| Eldepryl® U.K.         |           | 3.2                         |                            |
| <b>AUC</b>             |           |                             |                            |
| Zydis                  | 1.25      | 9                           | 3.2                        |
|                        | 2.5       |                             | 2.7                        |
| Eldepryl® U.S.         | 5 x 2     |                             | 4.3                        |
| Eldepryl® U.K.         |           | 10.5                        |                            |

Plasma exposure following Zydis selegiline and Eldepryl® tablets are compared in the following table (numbers represent Zydis/Eldepryl):

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| DOSING                 | ZYDIS DOSE<br>(mg) | STUDY NO.    |              |              |             |
|------------------------|--------------------|--------------|--------------|--------------|-------------|
|                        |                    | Z/SEL/95/023 | Z/SEL/95/003 | Z/SEL/96/014 | AN17933-101 |
| <b>C<sub>max</sub></b> |                    |              |              |              |             |
| acute                  | 1.25               | 2.5          | 1.6          | 1.2          | 3           |
|                        | 2.5                |              | 2.2          |              | 4           |
| multiple               | 1.25               |              |              | 0.8          | 2.3         |
|                        | 2.5                |              |              |              | 2.5         |
| <b>AUC</b>             |                    |              |              |              |             |
| acute                  | 1.25               | 1.4          | 0.9          | 0.6          | 0.8         |
|                        | 2.5                |              | 1.6          |              | 1.3         |
| multiple               | 1.25               |              |              | 0.6          | 0.6         |
|                        | 2.5                |              |              |              | 0.8         |

From these data and comparisons, the following were noted:

(a) plasma levels ( $C_{max}$ , AUC) of selegiline following acute dosing varied somewhat among studies. With the Zydis formulation,  $C_{max}$  ranged from 1.12 to 3.34 ng/mL and AUC ranged from  $\approx 0.5$  to 1.5 ng•hr/mL. With the Eldepryl<sup>®</sup> tablet,  $C_{max}$  ranged from  $\approx 0.5$  to 1.5 ng/mL and the AUC ranged from  $\approx 0.4$  to 1.9 ng•hr/mL. Inter-study variability was less at the 2.5 mg dose of Zydis; however, only 2 of the 4 studies assessed the 2.5-mg dose of Zydis selegiline.

(b) with acute dosing,  $C_{max}$  for selegiline was not proportionately higher (and in one case was notably lower) when selegiline was administered as a single 10-mg dose as compared to 5 mg b.i.d.

(c) with acute dosing, plasma  $C_{max}$  and AUC did not increase in a dose-proportionate manner with the Zydis formulation (1.25 and 2.5 mg).

(d) accumulation was observed with multiple dosing. However, the extent of accumulation was greater at Day 28 (Study Z/SEL/96//014) than at Day 10 (AN17933-101). As noted by Dr. Tandon, the half-life of selegiline (i.e., 1-4 hrs) is not consistent with accumulation.

(e) peak levels ( $C_{max}$ ) of selegiline were higher with the Zydis formulation (at both 1.25 and 2.5 mg) than with Eldepryl<sup>®</sup>, whereas, plasma AUCs for selegiline were actually less with the Zydis formulation than with Eldepryl<sup>®</sup> (except following an acute dose of 2.5 mg).

(f) plasma levels ( $C_{max}$ , AUC) of all major metabolites, i.e., N-desmethylselegiline, l-amphetamine, and l-methamphetamine, were markedly lower (0.2-0.4 times at 2.5 mg) following administration of Zydis selegiline as compared to Eldepryl<sup>®</sup>.

Based on these observations (in particular, the higher  $C_{max}$  with Zydis selegiline), there is interest in determining how the peak levels of selegiline achieved in the animal toxicity studies compare to the plasma exposure expected in humans. However, it is difficult to determine on what to base interspecies comparisons. Study AN17933-101 is the only multiple-dose study conducted using the clinical dosing regimen (i.e., b.i.d.) for Eldepryl<sup>®</sup>, and using the U.S. product. However, it is a parallel-grp design, not a crossover study. In addition, a comparison of the data from Studies

Z/SEL/96/014 and AN17933-101 suggested greater accumulation after 28 days than after 10 days of dosing, although plasma exposure (for selegiline) in Study Z/SEL/96/014 (based on acute-dose data) was less than in Study AN17933-101 (except for  $C_{max}$  for Eldepryl®). Taking these factors into consideration, it would appear that the animal exposure data should be compared to the acute dose  $C_{max}$  and AUC data from Study AN17933-101 multiplied by factors of 3 and 10, respectively.

#### Interspecies comparisons

Dog: In the original NDA for Eldepryl (NDA 19-334), TK data were not collected in the 1-yr oral toxicity studies in either rat or dog. In order to estimate plasma exposure to selegiline and metabolites in the 1-yr oral study in dog, the sponsor conducted a single-dose (3-mg/kg) pilot PK study in fed and fasted dog and a definitive 28-day bridging TK study in fasted dog.

The data from the pilot study in dog were compared to data from an acute-dose PK study in dog submitted in NDA 19-334. In the acute PK study, selegiline was administered i.v. (3 mg/kg) and p.o. (3, 10, and 30 mg/kg, in capsule form). Metabolites, desmethylselegiline, methamphetamine, and amphetamine, were quantitated; no assay was available at that time for quantitation of selegiline. Since the dietary status of the dogs in the original PK study was unknown, the sponsor conducted the acute-dose pilot study in both fed and fasted dogs. As noted by the sponsor, the levels of N-desmethylselegiline in the original PK study were too close to the LLOQ to provide useful data. Plasma levels ( $C_{max}$ , AUC) of amphetamine and methamphetamine obtained in the pilot study were somewhat higher (6-65%) in fasted than in fed dogs. Plasma AUCs for amphetamine and methamphetamine were lower (20-36%) in the pilot study (in both fed and fasted dogs) than in the original PK study. The plasma  $C_{max}$  for amphetamine was slightly higher (24-38%) in the pilot study in both fed and fasted dogs, whereas, the plasma  $C_{max}$  for methamphetamine was slightly higher (22%) in fasted dogs, but slightly lower (26%) in fed dogs compared to the original study. Based on these data, the sponsor concluded that the methodology used in the acute study adequately represented the conduct of the 1-yr study, and that the fasted condition was preferable (based on the interstudy comparison of plasma amphetamine exposure). Considering the fairly large interanimal variability in the exposure data, it is not clear that the small difference in plasma exposure between fed and fasted dogs reflected a real food effect.

In the 28-day TK bridging study, doses of 1, 4, and 16 mg/kg (no C grps) were administered to dogs (2/sex/grp) in capsule form. Clinical signs and other drug-related effects (i.e., body wt, clinical pathology) were fairly consistent with those observed in the 1-yr study. [No terminal studies were performed in the bridging study.] Additional food supplementation was provided in the bridging study due to body wt effects in the absence of decreases in food consumption. There was no indication that a similar strategy was used in the 1-yr study. The TK data for selegiline are summarized in the table below. The human data for selegiline (with the Zydis formulation at the maximum recommended human dose) were obtained from Study AN17933-101 and multiplied by factors based on the extent of accumulation observed in Study Z/SEL/96/014.

| SPECIES      | DOSE     | C <sub>max</sub><br>(ng/mL) | AUC<br>(ng•hr/mL)        |
|--------------|----------|-----------------------------|--------------------------|
| human        | 2.5 mg   | 4.47 (x 3 = 13)             | 2.44 (x 10 = 24)         |
| dog (n = 4)  | 16 mg/kg | 150<br>(range: 6.69-574)    | 151<br>(range: 39.2-459) |
| dog (n = 3)* | 16 mg/kg | 8.4<br>(range: 6.69-10.5)   | 48<br>(range: 39.2-52.2) |

\* means calculated with data from "outlier" removed.

The plasma exposure (C<sub>max</sub> and AUC) for selegiline estimated to have been achieved in the 1-yr oral study (at the HD) is lower than that estimated to be expected at the maximum recommended human dose (at steady state) of Zydis selegiline (with "outlier" data omitted from calculations). However, the interanimal variability was high, as was the intersubject variability in the clinical trials. The estimated maximum mean plasma C<sub>max</sub> achieved in the dog is fairly similar to that expected in humans (considering that the extent of accumulation in humans is a crude estimate). The plasma AUC is not a critical issue since in humans the Zydis formulation (at 2.5 mg) results in a lower AUC than the marketed oral formulation. [The maximum mean plasma AUC in dog exceeded that expected in humans.] Finally, there was no notable increase in toxicity in the published 3-mo transdermal toxicity in dog, compared to that observed in the 1-yr oral study even though plasma steady-state levels were considerably higher (≈4-fold) with transdermal selegiline. (No review of the 3-mo study could be found, although the study was summarized in the original submission of IND 50,279 [Somerset Pharmaceuticals].) Based on these observations, it would seem that the oral database in dog provides a reasonable assessment of the toxicity of Zydis selegiline.

Other species: no PK/TK bridging studies were conducted in rat, rabbit, or mouse.

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#### IV. GENERAL TOXICOLOGY

Nonclinical toxicology studies conducted under NDAs 19-334 (Eldepryl<sup>®</sup> tablets) and 20-647 (Eldepryl<sup>®</sup> capsules) were referenced in support of the NDA. No new toxicology studies were conducted.

One-year oral toxicity studies in Sprague-Dawley rat and Beagle dog were reviewed under NDA 19-334. The sponsor conducted a 28-day TK study in dog in order to provide an estimate of plasma exposure achieved in the original 1-yr oral toxicity study; this study is discussed in the Pharmacokinetics/Toxicokinetics section.

No TK studies were conducted in rat. An estimate of plasma exposure in the 1-yr oral rat study would have been helpful in evaluating the relevance of that study in support of the Zydis formulation. However, the differences in plasma exposure between the Zydis formulation and Eldepryl<sup>®</sup> are probably not large enough to warrant additional general toxicology (or TK) studies in the rat, particularly considering the information available in the dog.

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## V. GENETIC TOXICOLOGY

The genotoxicity studies conducted under NDAs 19-334 (Eldepryl<sup>®</sup> tablets) and 20-647 (Eldepryl<sup>®</sup> capsules) were referenced in support of the NDA. No new genotoxicity studies were conducted.

The following genotoxicity studies were submitted in the original NDA (19-334, information obtained from the Pharmacology/Toxicology Review, Jerry Cott, Ph.D., 12/3/84):

1. Human lymphocyte culture (Nat'l Inst. of Public Health, Budapest).
2. *in vivo* micronucleus assay (Nat'l Inst. of Public Health, Budapest).
3. Ames test (Huntingdon Research Center, England).
4. Ames test (Univ Delgi Studi di Milano).
5. Gene conversion in *saccharomyces cerevisiae* (Univ Delgi Studi di Milano).

The following genotoxicity studies were submitted in an amendment to NDA 19-334 (information obtained from the Pharmacologist Review of NDA 19-334, Barry N. Rosloff, Ph.D., 11/22/88):

1. Chromosomal aberration study in Sprague-Dawley rat (no laboratory specified).
2. *in vivo* micronucleus assay in mice (no laboratory specified).
3. Cell transformation assay (SHE cells) (no laboratory specified).

The following genotoxicity studies were submitted to NDA 20-647 (from the Review and Evaluation of Pharmacology/Toxicology Data; original review, Lois M. Freed, Ph.D., 3/16/96):

1. Chromosomal aberration assay in Sprague-Dawley rat (Laboratory of Pharmacology and Toxicology, Hamburg, Germany, 6/3/85).
2. Ames test (National Frederic Joliet-Curie Institute for Radiobiological Research, Budapest, Hungary).
3. *in vitro* chromosomal aberration assay in human lymphocytes (National Institute of Public Health, Budapest, Hungary).
4. *in vivo* micronucleus assay in rat (National Institute of Public Health, Budapest, Hungary).
5. Ames test (Univ Delgi Studi di Milano).
6. Gene conversion in *Saccharomyces cerevisiae* D<sub>4</sub> (Uiv Delgi Studi di Milano; 3 studies).
7. Non-programmed synthesis of DNA in human WI-38 cells (Univ Delgi Studi di Milano).
8. Ames test (Huntingdon Research Center, England).
9. *in vivo* micronucleus assay in mice (no laboratory specified).

Considering the time period in which these studies were conducted and Eldepryl<sup>®</sup> tablet approved (NDA 19-334), there was not as much regulatory emphasis placed on the genotoxicity studies as there is currently. When the battery of genotoxicity studies was submitted and reviewed under NDA 20-647 (Eldepryl<sup>®</sup> capsule), it was determined that the battery was inadequate. As noted in the pharmacology/toxicology review for NDA 20-647,

"Of the 7 studies submitted, only 2 (Ames test, *in vivo* chromosomal aberration assay in rats), were conducted under GLP. Although no increases in revertants (Ames test) or chromosomal aberrations (*in vivo* assay) were detected, there were methodological problems with both studies. In the Ames test, the concentrations were not sufficiently high since there were no signs of cytotoxicity or insolubility even at the highest concentrations. In the *in vivo* chromosomal aberration assay, only 50 metaphases were examined per animal (OECD guidelines recommend at least 100 metaphases/animal) and the HD exceeded the MTD in females and produced no signs of toxicity in males.

A complete battery of genotoxicity tests was not submitted. No acceptable *in vitro* mammalian gene mutation or chromosomal aberration assay was submitted, as recommended by the ICH guidelines. This, in addition to the deficiencies in the two GLP studies submitted, resulted in the lack of sufficient genotoxicity data to determine whether or not Selegiline is mutagenic and/or clastogenic. The sponsor should be asked to perform a complete genotoxicity battery (cf. ICH guidelines) postmarketing."

Therefore, the sponsor should conduct a complete battery of genotoxicity studies as a Phase 4 commitment.

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## VI. CARCINOGENICITY

The carcinogenicity studies conducted under NDAs 19-334 (Eldepryl<sup>®</sup> tablets) and 20-647 (Eldepryl<sup>®</sup> capsules) were referenced in support of the NDA. As noted in approved labeling for Eldepryl<sup>®</sup> capsules, the "Assessment of the carcinogenic potential of selegiline in mice and rats is ongoing". To date, the sponsor (Somerset Pharmaceuticals) has not provided electronic datasets that are needed for an independent evaluation of the data. However, since oral carcinogenicity studies of selegiline have been submitted and since in humans the plasma AUC for selegiline (and metabolites) with Zydys selegiline do not exceed that for Eldepryl<sup>®</sup> at therapeutic doses, no additional data are necessary.

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## VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY

Reproductive and developmental toxicology studies conducted under NDAs 19-334 (Eldepryl<sup>®</sup> tablets) and 20-647 (Eldepryl<sup>®</sup> capsules) were referenced in support of the NDA. No additional studies were conducted. Also, no TK bridging studies were conducted in either rat or rabbit; therefore, there is no estimate of the plasma drug exposure achieved in the oral studies conducted under NDAS 19-334 and 20-647.

The following reproduction studies were submitted in the original NDA (19-334; information obtained from the Pharmacology/Toxicology Review, Jerry Cott, Ph.D., 12/3/84):

1. Segment I study in rat (Univ. Degli Studi di Milano). This study was not considered adequate, in part, because animals were not dosed during the mating period.
2. Segment II study in rat (Semmelweis Univ Med Sch, Budapest). This study was not considered adequate due to the lack of sufficient details regarding the methods used to conduct fetal examinations.
3. Segment II study in rabbit (Univ. Degli Studi di Milano). This study was considered adequate. However, the study was conducted only in 10 rabbits/grp.

No Segment III study was submitted.

The following reproduction studies were submitted in an amendment to NDA 19-334 (information obtained from the Pharmacologist Review of NDA 19-334, Barry N. Rosloff, Ph.D., 11/22/88):

1. Segment II study in rat (8/18/87, Huntingdon Research Centre, Ltd., England). This study appeared to be considered adequate.
2. Segment III study in rat (2/5/87; Laboratorium fur Pharmakologie und toxikologie, Hamburg, Germany). There was a 70% mortality rate at the HD; however, it appears that this study was considered adequate.

Dr. Rosloff noted that the sponsor should provide justification for dose-selection in the Segment I study in rat (previously reviewed by Dr. Cott) and the Segment II study in rabbit since no dose-limiting effects were observed in either of these studies. Dr. Rosloff also requested "A statement concerning the conformity of these studies (Segment I study in rat, Segment II studies in rat and rabbit) to the GLP regulations..." be submitted.

The following reproduction studies were submitted to NDA 20-647 (from the Review and Evaluation of Pharmacology/Toxicology Data; original review, Lois M. Freed, Ph.D., 3/16/96):

1. Segment II study in rat (Huntingdon Research Center Ltd, GLP, 1986). The study report was not considered adequate due to the lack of summary incidence tables for fetal skeletal and

visceral findings. (This study may have been the same Segment II study reviewed by Dr. Rosloff under NDA 19-334, although the study dates differ.)

2. Segment II study in rat I (previously submitted to NDA 19-334, reviewed by Dr. Cott). This was a non-GLP study and was considered inadequate due, among other factors, a lack of detailed methodology and individual animal data, and an inadequate number of pregnant females per grp (i.e., 5-8)

3. Segment II study in rat II (previously submitted to NDA 19-334, reviewed by Drs. Cott and Rosloff). This study was not conducted according to GLP, and had similar deficiencies as the Segment II study in rat I.

4. Segment III study in rat (previously submitted to NDA 19-334, reviewed by Dr. Rosloff). This study was considered inadequate since it did not include an assessment of the reproductive capacity or the behavioral development of the F<sub>1</sub> generation.

From the information provided in the reviews of the reproduction studies conducted in support of NDAs 19-334 and 20-647, it is clear that an adequate battery of reproductive and developmental toxicology studies has not been conducted. However, one or more of the studies (e.g., the Segment II study in rat conducted by Huntingdon Research Center) may be adequate if the data were submitted in a form to allow review. The sponsor (Elan) has no access to the data submitted under NDA 19-334.

The importance of the  $\approx 2$ -fold increase in  $C_{max}$  with the Zydis formulation (compared to Eldepryl<sup>®</sup>) in humans in terms of effects on reproductive parameters is unknown. Data from a battery of reproduction studies are usually not sufficient to determine whether drug-related effects are related to  $C_{max}$  or AUC. Certainly, adverse effects (including teratogenicity) have been determined to be sensitive to peak drug levels as opposed to total exposure. For example, valproic acid has been reported to induce a sharp increase in the incidence of adverse fetal effects (e.g., exencephaly) when plasma levels are increased by  $<50\%$  (Nau H. Chapter 6, in: *Pharmacokinetics in Teratogenesis Vol 1*, Nau H, Scott WJ, Eds., CRC Press, Inc, Boca Raton, Florida, 1987, pg 100). The plasma levels of selegiline achieved in the oral reproductive toxicology studies (listed above) are unknown.

Considering the inadequacy of the available reproductive toxicology studies and the fact that peak levels of selegiline are higher with the Zydis formulation, the sponsor should conduct a complete battery of reproductive and developmental toxicology studies as a Phase 4 commitment.

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**VIII. SPECIAL TOXICOLOGY STUDIES**

Nonclinical special toxicology studies conducted under NDAs 19-334 (Eldepryl® tablets) and 20-647 (Eldepryl® capsules) were referenced in support of the NDA. The sponsor conducted a 4-wk + 2-wk buccal study in hamster in order to assess the local effects of Zydis selegiline.

**Study title:** A 4-week cheek pouch buccal toxicity study with Zelapar in hamsters, with a 2-week recovery period.

**Study no:** 340-027-99

**Volume #, page #:** Vol 1, pg 25

**Conducting laboratory and location:** ~~\_\_\_\_\_~~ **b(4)**

**Date of study initiation:** 9/2/99

**GLP:** Y

**QA report:** Y

**Drug, lot #, radiolabel, and % purity:** selegiline, lot no. 13458C043, purity data not provided.

**Formulation/vehicle:** Zelapar tablet (1.25 mg selegiline) ground with a mortar and pestle and solubilized in 1% phosphate buffered saline. Solution was prepared fresh daily.

**Methods**

The study was conducted in Golden Syrian hamsters obtained from ~~\_\_\_\_\_~~ **b(4)**

~~\_\_\_\_\_~~ The experimental design was summarized in the following sponsor's table:

| Group | Dose Material           | Total Number of Males/ Females | Selegiline Dose per Cheek Pouch   |                      | Selegiline Dose per Animal (mg/kg) | Selegiline Conc. (mg/mL) <sup>c</sup> | Zelapar Conc. (mg/mL) <sup>d</sup> |
|-------|-------------------------|--------------------------------|-----------------------------------|----------------------|------------------------------------|---------------------------------------|------------------------------------|
|       |                         |                                | (mg/m <sup>2</sup> ) <sup>a</sup> | (mg/kg) <sup>b</sup> |                                    |                                       |                                    |
| 1     | 1% w/v PBS <sup>e</sup> | 8/8                            | 0                                 | 0                    | 0                                  | 0                                     | 0                                  |
| 2     | Placebo Tablet          | 8/8                            | 0                                 | 0                    | 0                                  | 0                                     | 300                                |
| 3     | Selegiline              | 8/8                            | 2.4                               | 0.46                 | 0.93                               | 0.46                                  | 10                                 |
| 4     | Selegiline              | 8/8                            | 7.1                               | 1.4                  | 2.8                                | 1.4                                   | 30                                 |
| 5     | Selegiline              | 8/8                            | 24                                | 4.6                  | 9.3                                | 4.6                                   | 100                                |
| 6     | Selegiline              | 8/8                            | 71                                | 14                   | 28                                 | 14                                    | 300                                |
| 7     | 5% w/v SLS <sup>f</sup> | 3/3                            | 0                                 | 0                    | 0                                  | 0                                     | 0                                  |

<sup>a</sup>Assuming 134 g per hamster (determined from the average of all groups combined).  
<sup>b</sup>Assuming 134 g hamster = 0.0262 m<sup>2</sup>.  
<sup>c</sup>Dose volume was 1 mL/kg.  
<sup>d</sup>One Zelapar tablet weighs approximately 27 mg, and contains 1.25 mg of Selegiline.  
<sup>e</sup>PBS = Phosphate Buffered Saline  
<sup>f</sup>SLS = Sodium Lauryl Sulfate

The method of dosing was as follows:

Day 1: both cheek pouches were cleaned prior to dosing. The R pouch in all animals was abraded "...using two firm strokes of a 20 gauge brass wire bore cleaner"; abrasion was performed under anesthesia. Abrasion was only conducted on Day 1.

Days 1-28: selegiline, PC, or placebo test was applied to both cheek pouches of

each animal using an 18-gauge ball-tipped cannula attached to a 250 µL Hamilton syringe. "The cannula was gently inserted down to the most caudal portion of the right cheek pouch and the dose administered. The cannula was used to spread the dose over the mucosal surface, then withdrawn. This procedure was repeated on the left cheek pouch. In each animal, both cheek pouches received the same dose. PC animals received doses only on Days 1-6, 9, 12, 14, 16, 19, 21, 23, 26, and 28 due to local irritation.

3/sex/grp in Grps 1-6 were sacrificed on Day 6 and on Day 29; 2/sex/grp (Grps 1-6) were sacrificed following a 2-wk recovery period (i.e., on Day 42). 3/sex were treated with 5% sodium lauryl sulfate (SLS) as a positive control; these animals were sacrificed on Day 29.

Observations consisted of the following: mortality/clinical signs (twice daily), evaluation of local irritation (daily; irritation was graded on a scale of 0-3, with 0 = nonirritant, 1 = discoloration and/or slight sloughing, 2 = sloughing in several areas, 3 = ulceration), body wt and food consumption (prior to start of dosing and on study days 6, 15, 22, 29, 36, 42), gross pathology (a complete necropsy was conducted on all animals), histopathology (on the following tissues: entire L and R cheek pouch mucosa, 2 vertical cross sections of head (maxillae/mandible, labial junctions, gingival tissues, hard and soft palate, nasopharyngeal and nasal passages, tongue, larynx, esophagus, stomach, gross lesions; tissues were preserved in 10% neutral buffered formalin. For microscopic examination (performed by ~~XXXXXXXXXXXX~~), cheek pouches were embedded in paraffin and sectioned longitudinally [2 sections] through the apex of the cheek pouch.

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## Results

There were no unscheduled deaths and no clinical signs clearly related to drug. Mucosal irritation was only observed in animals treated with SLS. Mean mucosal irritation scores (MMIS; calculated as the sum of all scores per grp divided by the no. of animals per grp and multiplied by the no. of days of examination [i.e., 28]) were 1.6-1.7 in males and 1.3 in females receiving SLS; there was no difference in MMISs between abraded and nonabraded pouches. (According to the sponsor categories, MMIS of 1.1-2.0 reflect a "moderate irritant". Body wt and food consumption were not significantly affected by selegiline in either males or females.

No drug-related gross lesions were detected. No drug-related microscopic changes in cheek pouches were detected in animals treated with selegiline. In contrast, evidence of "chronic active inflammation, squamous epithelial hyperplasia and hyperkeratosis" was detected in the cheek pouches of animals receiving SLS. The data are summarized in the tables below (incidences in each cell are for Day 6 [top], Day 29 [middle], recovery [bottom]). Inflammation of the larynx was observed to a greater extent in HDM and in 1/2 females at each of the two highest doses. According to the pathologist's report, "This small accumulation of lymphocytes in the ventral larynx is a common spontaneous change in rodents and is not considered related to compound administration."

**Males**

| TISSUE        | FINDING                | [SELEGILINE] (mg/mL) |         |      |     |     |     | 5% SLS |
|---------------|------------------------|----------------------|---------|------|-----|-----|-----|--------|
|               |                        | 0 (sal)              | 0 (tab) | 0.46 | 1.4 | 4.6 | 14  |        |
| R cheek pouch | inflammation           | 1/3                  | 0/3     | 2/3  | 1/3 | 2/3 | 0/3 | --     |
|               |                        | 0/3                  | 0/3     | 0/3  | 0/3 | 1/3 | 0/3 | 3/3    |
|               |                        | 0/2                  | 0/2     | 0/2  | 0/2 | 1/2 | 1/2 | --     |
|               | hyperkeratosis         | 0/3                  | 1/3     | 1/3  | 0/3 | 0/3 | 1/3 | --     |
|               |                        | 0/3                  | 0/3     | 0/3  | 0/3 | 0/3 | 0/3 | 3/3    |
|               |                        | 0/2                  | 0/2     | 0/2  | 0/2 | 0/2 | 0/2 | --     |
|               | epithelial hyperplasia | 0/3                  | 0/3     | 0/3  | 0/3 | 0/3 | 0/3 | --     |
|               |                        | 0/3                  | 0/3     | 0/3  | 0/3 | 0/3 | 0/3 | 3/3    |
|               |                        | 0/2                  | 0/2     | 0/2  | 0/2 | 0/2 | 0/2 | --     |
| L cheek pouch | inflammation           | 0/3                  | 0/3     | 1/3  | 0/3 | 0/3 | 0/3 | --     |
|               |                        | 0/3                  | 0/3     | 0/3  | 1/3 | 0/3 | 0/3 | 3/3    |
|               |                        | 0/2                  | 0/2     | 0/2  | 0/2 | 1/2 | 0/2 | --     |
|               | hyperkeratosis         | 0/3                  | 0/3     | 0/3  | 0/3 | 0/3 | 0/3 | --     |
|               |                        | 0/3                  | 0/3     | 0/3  | 0/3 | 0/3 | 0/3 | 3/3    |
|               |                        | 0/2                  | 0/2     | 0/2  | 0/2 | 0/2 | 0/2 | --     |
|               | epithelial hyperplasia | 0/3                  | 0/3     | 0/3  | 1/3 | 0/3 | 0/3 | --     |
|               |                        | 0/3                  | 0/3     | 0/3  | 0/3 | 0/3 | 0/3 | 3/3    |
|               |                        | 0/2                  | 0/2     | 0/2  | 0/2 | 0/2 | 0/2 | --     |
| larynx        | inflammation           | 1/3                  | 0/3     | 0/3  | 1/3 | 0/3 | 0/3 | --     |
|               |                        | 0/3                  | 0/3     | 0/3  | 1/3 | 0/3 | 1/3 | 1/3    |
|               |                        | 0/2                  | 0/2     | 0/2  | 0/2 | 0/2 | 2/2 | --     |

**Females**

| TISSUE        | FINDING                | [SELEGILINE] (mg/mL) |         |      |     |     |     | 5% SLS |
|---------------|------------------------|----------------------|---------|------|-----|-----|-----|--------|
|               |                        | 0 (sal)              | 0 (tab) | 0.46 | 1.4 | 4.6 | 14  |        |
| R cheek pouch | inflammation           | 1/3                  | 0/3     | 2/3  | 1/3 | 1/3 | 0/3 | --     |
|               |                        | 0/3                  | 0/3     | 0/3  | 0/3 | 0/3 | 0/3 | 3/3    |
|               |                        | 0/2                  | 1/2     | 0/2  | 0/2 | 0/2 | 0/2 | --     |
|               | hyperkeratosis         | 0/3                  | 0/3     | 2/3  | 0/3 | 0/3 | 1/3 | --     |
|               |                        | 0/3                  | 0/3     | 0/3  | 0/3 | 0/3 | 1/3 | 3/3    |
|               |                        | 0/2                  | 0/2     | 0/2  | 0/2 | 0/2 | 0/2 | --     |
|               | epithelial hyperplasia | 0/3                  | 0/3     | 0/3  | 0/3 | 0/3 | 0/3 | --     |
|               |                        | 0/3                  | 0/3     | 0/3  | 0/3 | 0/3 | 0/3 | 3/3    |
|               |                        | 0/2                  | 0/2     | 0/2  | 0/2 | 0/2 | 0/2 | --     |
| L cheek pouch | inflammation           | 0/3                  | 0/3     | 0/3  | 1/3 | 0/3 | 0/3 | --     |
|               |                        | 0/3                  | 0/3     | 0/3  | 0/3 | 1/3 | 0/3 | 3/3    |
|               |                        | 0/2                  | 1/2     | 0/2  | 0/2 | 0/2 | 0/2 | --     |
|               | hyperkeratosis         | 0/3                  | 0/3     | 0/3  | 0/3 | 0/3 | 0/3 | --     |
|               |                        | 0/3                  | 0/3     | 0/3  | 0/3 | 0/3 | 0/3 | 3/3    |
|               |                        | 0/2                  | 0/2     | 0/2  | 0/2 | 0/2 | 0/2 | --     |
|               | epithelial hyperplasia | 0/3                  | 0/3     | 0/3  | 0/3 | 0/3 | 0/3 | --     |
|               |                        | 0/3                  | 0/3     | 0/3  | 0/3 | 0/3 | 0/3 | 3/3    |
|               |                        | 0/2                  | 0/2     | 0/2  | 0/2 | 0/2 | 0/2 | --     |
| larynx        | inflammation           | 1/3                  | 1/3     | 0/3  | 0/3 | 0/3 | 0/3 | --     |
|               |                        | 2/3                  | 1/3     | 0/3  | 0/3 | 0/3 | 0/3 | 1/3    |
|               |                        | 0/2                  | 0/2     | 0/2  | 0/2 | 1/2 | 1/2 | --     |

**Summary and conclusions**

The sponsor conducted a buccal study in Golden Syrian hamster in order to assess the potential of selegiline to produce local irritation and/or cellular changes to the buccal mucosa. Selegiline (1.25 mg clinical formulation) was applied to the cheek pouches at doses of 0.46-14 mg/kg

(concentrations: 10-300 mg/mL) for either 6 or 29 days. The right cheek pouch was abraded on Day 1 only. Separate grps of animals received saline, placebo tablet, or positive control (sodium lauryl sulfate, SLS). Animals receiving SLS were not dosed daily due to local irritation. Additional grps were followed for a 2-wk recovery period. A complete necropsy was conducted on all animals, and selected tissues were examined microscopically (cheek pouches, cross-sections of head, nasopharyngeal and nasal passages, tongue, larynx, esophagus, stomach, and gross lesions). There were no unscheduled deaths, no clinical signs clearly related to drug, no drug-related effects on body wt or food consumption, or drug-related gross lesions. No drug-related microscopic changes were observed in cheek pouches or other tissues examined. Inflammatory changes in the larynx were more frequently observed in HDM (and also in 1 F/grp at each of the two highest doses), however, this finding was not considered drug-related by the sponsor.

It is unfortunate that the sponsor did not collect TK data during this study, particularly considering the negative findings. Such data would have been helpful in documenting the extent of absorption through the cheek pouch mucosa.

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## IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS

### Conclusions

The sponsor provided sufficient data to justify the use of the oral toxicity data in dog submitted under NDA 19-334 to be used in support of the Zydis formulation.

However, no bridging data were provided for the other animal species used in nonclinical studies conducted in support of the tablet/capsule formulation (NDAs 19-334, 20-647). The lack of these data makes it difficult to evaluate the adequacy of the oral nonclinical studies (including reproductive toxicity, carcinogenicity) conducted in these species to assess human risk relative to the Zydis formulation. Since the plasma AUC for selegiline was slightly lower with the Zydis formulation (compared to Eldepryl<sup>®</sup>, 5 mg b.i.d.) in humans, there would be no need to bridge to the oral carcinogenicity studies since tumorigenic effects are considered to reflect total exposure as opposed to peak levels (i.e.,  $C_{max}$ ). However, reproductive toxicity may be sensitive to  $C_{max}$ . The sponsor provided no data by which to determine whether or not sufficient exposure to selegiline was achieved in the reproductive toxicity studies. Even if the sponsor had provided bridging studies, the reproductive toxicity studies submitted to NDA 19-334 were not adequate. Therefore, the sponsor should be asked to conduct a complete battery of reproductive toxicology studies as a Phase 4 commitment.

The sponsor should also be asked to conduct a complete battery of genotoxicity studies as a Phase 4 commitment, considering the inadequacy of the genotoxicity studies submitted under NDAs 19-334 and 20-647.

### Recommendations

From a pharmacology/toxicology standpoint, there is no objection to the approval of the NDA. However, it is recommended that the sponsor commit to conducting a complete battery of reproductive and developmental toxicology studies and a complete battery of genotoxicity studies post approval (cf. *Guideline for Industry - Detection of Toxicity to Reproduction for Medicinal Products*; ICH-S5A, Sept 1994; *A Standard Battery for Genotoxicity Testing of Pharmaceuticals*; ICH-S2B, Jul 1997). The *in vivo* studies should be conducted using a route of administration that will result in plasma exposure to selegiline and major metabolites exceeding those expected in humans at the maximum recommended clinical dose.

### Labeling recommendations

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b(5)

1   Page(s) Withheld

       Trade Secret / Confidential (b4)

  ✓   Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

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