

### 11.5.2 Collagen vascular disease study 21-91-901

this uncontrolled, open-label study 31 subjects (patients with cutaneous ulcers secondary to various collagen vascular diseases) received clz 50 mg bid for up to 8 weeks, with optional downtitration to half this dose. AE occurred in 48%. These included headache (36%), palpitation/tachycardia (10%), and one report each of tinnitus and occult fecal blood. Approximately 19% of patients dropped out due to AE.

### 11.6 Safety in Diabetes

#### 11.6.1 Diabetes study 21-91-002

In this uncontrolled, open-label study 44 subjects (patients with diabetic polyneuropathy) received cilostazol 100 mg bid (with optional downtitration to one-half or three-quarters this dose) for 12 weeks. The overall AE rate was 11%. The individual events were 2 incidences each of headache and palpitation, and 1 incidence each of rash, headache, bleeding gastric ulcer, nausea, vomiting, and increased hepatocellular enzymes.

#### 11.6.2 Diabetes study 21-92-003

In this study there has thusfar been one case of pancytopenia (decreased RBC, WBC, and platelet levels) in a subject treated with clz 100 mg/d for 12 weeks. This subject reportedly had shown gradual decreases in platelet and WBC levels prior to treatment. This patient died 6 months after discontinuing drug.

Two subsections of this ongoing study (i.e. 21-92-003-A and 21-92-003-B) are here combined into one discussion. In this placebo-controlled, double-blind study patients (subjects with diabetic polyneuropathy) receive either cilostazol (100-200 mg/d), or placebo for 12-24 weeks. Thusfar the experience in 338 patients has been characterized, although the entirety of the data has not been unblinded. Combining all treatment groups, 16% have reported AE, and 8% have dropped out due to AE. The most frequent non-serious AE were reportedly headache, palpitation/tachycardia, digestive disorders, and bleeding and clotting disorders.

#### 11.6.3 Diabetes study 21-93-001

In this placebo-controlled, double-blind study 112 subjects (patients with diabetes mellitus and serum triglyceride levels  $\geq 150$  mg/dl) were given cilostazol 100 mg bid or placebo for 12 weeks. The goal was to assess drug effect on lipids, uric acid, and glucose tolerance. AE rates were significantly higher in the cilostazol group (36%) than in the placebo group (7%). there were no significant differences in fasting blood glucose levels or HbA<sub>1c</sub> levels in the two groups.

#### 11.6.4 Diabetes study 21-93-002

This is an ongoing study which was not yet evaluated by the sponsor at the time of the NDA data cutoff. In this uncontrolled, open-label study 60 patients with diabetic polyneuropathy are to receive cilostazol 100 mg bid for more than 24 weeks. With 76 patients observed on an interim basis, 6.6% dropped out for AE.

#### 11.7 Safety in Nephritis

##### 11.7.1 Nephritis study 21-89-004

In this uncontrolled, open-label study 62 subjects (patients with chronic glomerulonephritis) received cilostazol 50 mg bid (with optional uptitration to twice this dose) for 24 weeks. Cilostazol was reportedly ineffective in correcting renal dysfunction. AE were reported in 23 patients (37%), 17 of whom dropped out. There was a 29% rate of headache. Other AE were nausea, epigastric pain, heartburn, edema, facial redness, allergy, and diarrhea.

##### 11.7.2 Nephritis study 21-89-005

In this uncontrolled, open-label study 55 subjects (patients with chronic glomerulonephritis) received cilostazol 25-100 mg bid for more than 24 weeks. Cilostazol was reportedly ineffective at correcting renal dysfunction. AE occurred in 45% of patients: there were 20 reports of headache, 3 of palpitation and tachycardia, and 1 each of nausea, gastric discomfort, hepatic impairment, skin eruption, and insomnia. Drug was discontinued in 24% for AE, whereupon the events resolved.

##### 11.7.3 Nephritis study 21-90-005

In this uncontrolled, open-label study 24 subjects (patients with glomerulonephritis) received cilostazol 100 mg bid for 24 weeks. Cilostazol was reportedly ineffective in correcting renal function. AE were reported in 24% of patients: there were 4 reports of headache, 1 each of palpitation, nausea, blood pressure elevation, and leg edema. One patient (with headache) dropped out because of an AE.

#### 11.8 Safety in Neurologic diseases

##### 11.8.1 Neurological disease study 21-88-001

In this placebo-controlled, double-blind study 593 subjects (patients with symptomatic sequelae of recent cerebral infarction) received<sup>36</sup> either placebo or clz 100 mg bid for 8 weeks. Cilostazol

<sup>36</sup> it was not explicitly stated that the treatment assignment was to be random.

reportedly had no beneficial effect on post-stroke symptoms. AE were reported in 17% of the cilostazol group vs 7% of the placebo group. The most frequent AE in the cilostazol group were headache (6%) and palpitation (3%).

#### 11.8.2 Neurological disease study 21-88-004

In this aspirin-controlled, double-blind, parallel-group study 78 subjects (patients with >2 TIAs in the prior 3 months) were treated with cilostazol 100 mg bid or aspirin 100 mg/day for not less than 6 months and up to 12 months. The number of recurrent TIAs was reportedly less in the cilostazol group. AE reportedly occurred in 13% of the cilostazol group and 11% of the aspirin group.

#### 11.8.3 Neurological disease study 21-88-007

In this uncontrolled, open-label study 12 subjects (patients at least one month status post cerebral infarction) received cilostazol 100 mg bid for 4 weeks. Cerebral blood flow was estimated using an intravenous xenon method. Cilostazol showed a nonsignificant trend towards increasing cerebral blood flow. It was reported that no apparent AE occurred during the study.

#### 11.8.4 Neurological disease study 21-88-008

In this uncontrolled, open label study 12 subjects (patients at least one month status post cerebral infarction) received cilostazol 100 mg bid for 4 weeks. Pre- and post-treatment estimates of blood flow in the common and external carotid arteries were obtained with Doppler ultrasound. It was asserted that cilostazol was associated with increased extracranial arterial blood flow. Headache was observed in three cases.

#### 11.8.5 Neurological disease study 21-89-001

In this ticlopidine-controlled, open-label study 20 elderly (mean age 73 years) brain ischemia patients (cerebral infarction or transient ischemic attack) were treated with oral cilostazol at 150 mg/d (half received 50 mg tid and half got 75 mg bid), or ticlopidine 200 mg/d for 4 weeks. Eight adverse events were reported, including increased BUN, gastrointestinal bleeding, anemia, and leukocytosis.

#### 11.8.6 Neurological disease study 21-89-006

In this uncontrolled, open-label study 6 subjects (patients with TIA) received cilostazol 100 mg bid for 12 months. In-vitro antiplatelet effects were reportedly observed. No adverse events were reported.

### 11.8.7 Neurological disease study 21-91-001

This ongoing, placebo-controlled, double-blind study enrolled 1095 subjects (patients 1-6 months status post cerebral infarction) thusfar have received clz 100 mg bid<sup>37</sup>. The goal is to assess the effect of cilostazol on the recurrence of cerebral infarction in approximately 1100 such patients treated for 1-5 years. Enrollment was completed in 3/96; the majority are expected to be followed for 1-2 years.

It was reported that 83 subjects (of undefined treatment assignment) have thusfar dropped out for AE, but safety results have, by and large, not been made available at the time of the NDA data cutoff. No unblinded safety analyses have yet been submitted (as of the first safety update). It is reported that an interim safety analysis led the Safety Monitoring Committee to allow the continuation of the study, on safety grounds.

### 11.8.8 Neurological disease study 21-91-003

In this still-blinded, placebo-controlled, double-blind study 299 subjects (adult patients with chronic cerebral insufficiency) received either placebo or clz 50-100 mg bid for 8 weeks<sup>38</sup>. The submitted safety data are not yet interpretable given that randomization codes were not opened. Combining both treatment groups, headache and palpitation were the most AE, and 43 subjects dropped out due to one or another AE.

### 11.8.9 Neurological disease study 21-92-001

In this uncontrolled, open-label study 19 subjects (patients with stroke) received clz 100 mg bid for 4 weeks. In-vitro evaluation reportedly showed that cilostazol inhibited the platelet aggregation induced by low shear stress. Headache was reported in 4 patients, palpitation in 3 patients, gastric discomfort in 1 patient, and whole body edema in 1 patient. Five patients were withdrawn from the study due to AE.

### 11.8.10 Neurological disease study 21-92-002

In this ongoing, uncontrolled, open-label study 16 subjects (patients with chronic cerebrovascular insufficiency) have thusfar received 100 mg tablets bid for 12 weeks (6 months if possible). Cerebral blood flow is to be estimated using SPECT before and 8-12 weeks after the drug's initiation. Each of 2 patients has thusfar reported headache, nausea, and/or rash. Two subjects have thusfar dropped out for AE (rash and headache).

<sup>37</sup> it was not explicitly stated that the treatment assignment was to be random.

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11.8.11 **Neurological disease study 21-93-003**

this ongoing, uncontrolled, open-label study 24 subjects (patients with chronic cerebrovascular insufficiency) have thusfar received clz 100 mg bid (exposure duration to be 12-24 weeks). Cerebral blood flow is to be estimated using SPECT before and 12 weeks after the drug's initiation.

Reportedly no serious AE were observed. Eleven AE were reported, headache being most frequent. Five subjects have dropped out for AE. No further details have thusfar been provided.

11.8.12 **Neurological disease study G-16**

In this uncontrolled, open-label study 64 subjects (patients stable at one month post cerebral infarction) received clz 100-300 mg/d (either 50 mg bid, 50 mg tid, or 100 mg tid) for 4 weeks. CLZ was asserted to have shown putative benefits on post-stroke symptomology. An increased heartrate was observed at all doses. There were reportedly no AE at the 100 mg/d dose.

At 150 mg/d there were 2 reports each of nausea and appetite loss, and 1 report each of insomnia and worsened diabetes. At 200 mg/d there was 1 report each of headache, palpitation, stomach discomfort, and liver function abnormality (with no CRF record of followup observations) in the setting of suspected ethanol overuse in patient #22 (SGOT rise from 33 to 55 IU, alkaline phosphatase rise from 90 to 111 IU, and LDH increase from 210 to 294 IU). At 300 mg/d there was 1 report each of thalamic pain, and liver function abnormality (with no CRF record of followup observations) in patient #47 (SGPT rise from 17 to 88, and LDH increase from 274 to 440).

11.8.13 **Neurological disease study G-17**

In this uncontrolled, double-blind study 192 subjects (patients with transient ischemic attacks or status post cerebral infarction) were randomized to one of 3 doses of clz (100, 150 or 200 mg/d) for 8 consecutive weeks. There was no significant drug effect on neurological symptoms.

Among 182 evaluated patients the AE rate (i.e. 12%) was reportedly not related to dose. One patient died of ruptured esophageal varices on treatment day 13. The most frequently reported AE (3 reports each) were headache, nausea/vomiting, and tachycardia. There were 2 reports each of dizziness, orthostatic dizziness, and soft stool. There was one case each of vertigo, insomnia, diarrhea, skin eruption, itching, subcutaneous bleeding, and urinary frequency. Abnormal laboratory values were reported in 16%.

The sponsor describes difficulty retrieving the laboratory reference ranges used in the older Japanese studies such as this, but reports that current standards used in Japan are: RBC count in a male:  $4.27-5.70 \times 10^6/\text{mm}^3$ ; RBC count in a female:  $3.76-5.00 \times 10^6/\text{mm}^3$ ; platelet count 130-369

$\bar{X}$   $10^3/\text{mm}^3$ ;  $\gamma$ -GTP level 0-59 U/L; WBC in a male: 3.9 - 9.8  $\times 10^3/\text{mm}^3$ , WBC in a female: 3.5 - 9.1  $\times 10^3/\text{mm}^3$ ; Fibrinogen: 200-400 mg/dL; SGOT 8-33 U/L; SGPT 4-45 U/L.

Patient 33-2 (200 mg/d clz) had, as observed at week 8, an increase in alkaline phosphatase from 1.9 to 4.1 IU, an increase in  $\gamma$ -GTP from 34 to 265 IU, and an increase in triglyceride from 305 to 559 mg/dL. There is reportedly no documentation of followup.

Patient 7-2 (200 mg/d clz) had an isolated fall in RBC count from 4.19 to 3.76  $\times 10^6/\text{mm}^3$  without any associated reduction in hemoglobin or hematocrit. The RBC count had risen to 3.89  $\times 10^6/\text{mm}^3$  by week eight. There is reportedly no record of followup observations.

Patient 18-5 (150 mg/d clz) had an isolated, mild fall in RBC count from 4.11 to 3.69  $\times 10^6/\text{mm}^3$  without any associated reduction in hemoglobin or hematocrit. There is reportedly no record of followup observations.

Patient 21-3 (200 mg/d clz) had the following transient increases in liver function parameters: SGPT increased from 9 to 23 U, and  $\gamma$ -GTP increased from 26 to 51 U. These values reportedly returned to normal by 2 months post-discontinuation of drug.

Patient 26-1 (150 mg/d clz) had the following increases in liver function parameters: SGOT increased from 15 to 48 U, SGPT increased from 15 to 55 U, LDH increased from 208 to 221 U,  $\gamma$ -GTP increased from 57 to 119 U. There were reportedly no "physical AE" at the time of these abnormalities, and no record of followup observations.

Patient 38-5 (200 mg/d clz) had a decrease in platelet count from 186 to 115  $\times 10^3/\text{mm}^3$ . There were reportedly no "physical AE" at the time of this abnormality, and no record of followup observations.

#### 11.8.14 Neurological disease study G-18

In this positive-controlled, double-blind study 305 subjects (patients with a variety of cerebrovascular disorders) were randomized (1:1) to cilostazol 100 mg/d or trapidil 300 mg/d for 8 weeks.

AE among cilostazol patients were as follows: headache (2.7%), urticaria-like rash/redness (2%), weakness/numbness (1.4%), diarrhea (1.4%), and one case each of mouth numbness, anorexia, increased serum urate, hypertension, fever, phlebitis, and hematuria.

There were 6 dropouts for AE among cilostazol-treated patients: three for headache (patients 8-2, 3, and 54-4), two for skin eruption (patients 4-6, and 18-3), and one for phlebitis (patient 4-5).

The following were laboratory findings reported among those who did not drop out.

renal abnormality case:

Patient 34-4 developed a treatment-associated further elevation of baseline elevated creatinine (from 1.5 to 2 mg/dl).

Leukopenia cases:

During exposure to clz 100 mg/d, patient 46-6, a 60 year old male, developed an isolated<sup>39</sup> leukopenia (leukocyte count fell from  $6.3 \times 10^3/\text{mm}^3$  at week four, and then to  $1.9 \times 10^3/\text{mm}^3$  at week 8). Two followups were reported. Leukopenia persisted with a count of  $2.0 \times 10^3/\text{mm}^3$  at each of two followups (conducted at 2 and roughly 4 weeks after drug discontinuation). No subsequent clinical observations were reported.

Patient 48-2, a 54 year old male, developed a transient, isolated leukopenia (leukocyte count fell from a baseline of  $3.8 \times 10^3/\text{mm}^3$  at week 8, and then returned to  $4.1 \times 10^3/\text{mm}^3$  about a week after drug discontinuation).

Patient 38-6, a 75 year old female, developed a transient isolated leukopenia (leukocyte count fell from 3.2 at pre-treatment to  $2.9 \times 10^3/\text{mm}^3$  at weeks 4 and 8) with leukocyte count returning to  $3.3 \times 10^3/\text{mm}^3$  by 3 days after drug discontinuation.

Patient 53-3 developed slight worsening of pre-treatment leukopenia (leukocyte count fell from  $2.9 \times 10^3/\text{mm}^3$  to  $2.8 \times 10^3/\text{mm}^3$ ), in association with a fall in erythrocyte count from  $3.92 \times 10^6/\text{mm}^3$  to  $3.61 \times 10^6/\text{mm}^3$ . Both findings were made at the end of the trial.

Patient 27-2 developed an isolated leukopenia (leukocyte count fell from  $8.0 \times 10^3/\text{mm}^3$  at pre-treatment to  $3.9 \times 10^3/\text{mm}^3$ ). This finding was made at the end of the trial.

Anemia cases:

Patient 25-4 developed a mild anemia (Hb fell to 12.9 g/dl, Hct to 38.7%, and erythrocyte count to  $3.95 \times 10^6/\text{mm}^3$ ).

Patient 33-5 developed a mild anemia (Hb fell to 13.1 g/dl, Hct to 38.9%, and erythrocyte count to  $3.84 \times 10^6/\text{mm}^3$ ).

Patient 56-2 developed anemia (Hb fell to 10 g/dl, Hct to 30.5%, and erythrocyte count to  $4 \times 10^6/\text{mm}^3$ ). These findings first became apparent mid-way through the trial.

<sup>39</sup> i.e., without other laboratory evidence of hematologic abnormality.

Patient 56-3 developed anemia (Hb fell to 11.1 g/dl, Hct to 34.2%, and erythrocyte count to  $3 \times 10^6/\text{mm}^3$ ). These findings were made at the end of the trial.

Cases of other hematologic findings:

Patient 38-3, a subject with pre-treatment APTT abnormality which persisted (ranging from 22.2-23.5 seconds), had a pre-treatment fibrinogen level of 129 mg/dl which fell to 87 mg/dl at week 8.

Hepatic abnormality cases:

Patient 42-1, a 50 year old male receiving clz 100 mg/d, developed treatment-associated liver function abnormalities by week 8. Followup was obtained 3 weeks after discontinuation of drug. SGOT peaked at 74 U, and decreased to 43 U at post-discontinuation followup. SGPT rose to a peak of 110 U, decreasing to 48 U at followup. Alkaline phosphatase was observed at 3.1 KAU and persisted at this level through followup. The  $\gamma$ -GTP peaked at 120 U, and decreased to 76 U by followup.

Patient 14-1, a subject with pre-treatment elevation of SGPT developed a treatment-associated, mild increase in SGOT (to 35U) while SGPT remained little changed.

Patient 30-2, a subject with pre-treatment elevation of serum bilirubin, developed a slight increase in  $\gamma$ -GTP (to 40 U) during drug exposure, although bilirubin became normal.

Patient 33-4 developed an elevated LDH (to 407 U) while total protein transiently dropped to just below normal level. The LDH finding first became apparent at the trial's end.

Patient 37-1, a subject with broad pre-treatment elevations of liver function tests (SGOT, SGPT, and  $\gamma$ -GTP) developed slight, treatment-associated further increases in these levels (SGOT to 68 U, SGPT to 58 U, and  $\gamma$ -GTP to 58 U) by the end of the trial.

Patient 37-4 developed an isolated, mild elevation of LDH to 233 U.

Patient 38-2, a subject with pre-treatment elevation of SGOT, developed a slight treatment-associated further increase in SGOT (to 38 U) and elevation of  $\gamma$ -GTP first appearing at week and ultimately rising to 76 U.

Patient 38-3, a subject with pre-treatment elevations of liver function tests (LDH and total bilirubin) developed a treatment-associated further rise in LDH to 472 U while total bilirubin normalized.

Patient 39-3 (a subject with pre-treatment elevation of SGOT, SGPT, and  $\gamma$ -GTP) developed treatment-associated further increase of SGPT (to 66 U), and transient increase of alkaline phosphatase (to 122 IU).

Patient 39-5 developed treatment-associated further elevation of baseline elevated  $\gamma$ -GTP (from 78 to 90 U).

Patient 49-6 developed a treatment-associated persisting elevation of LDH (to 543 U/L), and transient elevations of SGOT (to a maximum of 152 U) and SGPT (to a maximum of 67 U).

Patient 50-4 developed transient, treatment-associated further elevation of baseline elevated LDH (from 379 to a maximum of 648 U/L).

Patient 54-1 developed treatment-associated elevations of SGOT (to 53 U) and SGPT (to 76 U).

Patient 56-2 developed transient, treatment-associated further elevation of baseline elevated LDH (from 368 to a maximum of 424 U/L).

#### 11.8.15 Neurological disease study G-19

In this uncontrolled, open-label study 26 subjects (patients with a variety of cerebrovascular disorders) received cilostazol 50 mg once daily for 8 consecutive weeks. There were no dropouts for AE. One patient had small LDH rise from a normal level of 433 to 482 at week 8. Another patient had SGOT, SGTP, and LDH levels which were transiently elevated at treatment week 4, but which returned to normal by week 8.

#### 11.8.16 Neurological disease study G-20

In this uncontrolled, open-label study 73 subjects (patients with a variety of cerebrovascular disorders) received cilostazol 50 mg bid for at least 56 weeks. Three patients discontinued because of AE: these were one case each of upper abdominal pain, palpitation, and subcutaneous bleeding (without evidence of generalized bleeding tendency). Each of these AE resolved in association with discontinuation of drug. Ten patients had abnormal laboratory values during treatment. Four of these were clinically unimportant, and generally isolated changes in antithrombin III levels. The 6 other laboratory changes were reportedly all mild or transient (e.g. such things as a mild, and transient hemoglobin reduction without abnormality of hematocrit or thrombocyte count in patient #1).

### 11.8.17 Neurological disease study G-21

this uncontrolled, open-label study 75 subjects (patients with a variety of cerebrovascular disorders) received cilostazol 50 mg/d cilostazol granules for 8 weeks. Three subjects dropped out because of AE (these being headache, congestion and gastrointestinal (GI) complaints, and "stomach ache"), and in each case the event resolved in association with drug discontinuation. AE overall were reported in 11% of subjects. The most frequent AE (for which there were 2 cases each) were headache or "heavy feeling of head", vertigo, and congestion. Various GI complaints, and minimal hyperuricemia were the other reported AE.

Nine patients had treatment-associated laboratory test abnormalities, reportedly none of which were clinically important. Mild increases in alkaline phosphatase occurred in 2 subjects. There was also one case of slight blood sugar elevation.

One male subject (#44) had a slight elevation of SGPT (to levels which some analysts would consider normal for a male) in association with a mild elevation of LDH (for which the pre-treatment LDH already approached abnormally high levels).

Another male subject (#23) had slight elevations of SGOT and SGPT (each rising to levels which some analysts would consider normal for a male) in association with an elevation of the nonspecific marker,  $\gamma$ -GTP, to 128 U/L (roughly twice the upper limit of normal).

Fibrinogen levels increased in 2 cases (to levels of 430-470 mg/dl), and decreased to 163 mg/dl in 1 case without any associated clinical phenomena causing any of these subjects to drop out. No thrombotic or hemorrhagic sequelae were reported.

## 11.9 Other International safety data

Japanese pre-market clinical studies 1086 subjects were exposed to open label or double-blind cilostazol at 25-300 mg/d, generally for 8 weeks. The 100 mg/d dose was investigated for up to 1 year. There was one death, secondary to ruptured esophageal varices. In 6 Asian (non-Japanese) post-marketing clinical trials 12 patients received CLZ 200 mg/d for 3 weeks; 12 healthy subjects received CLZ 100- 200 mg/d for 4 days; 21 patients with PAD received either placebo or CLZ 200 mg/d for 12 weeks; 85 diabetics with PAD were exposed to CLZ 200 mg/d for 8 weeks; 119 patients received CLZ 200 mg/d for 6 weeks, and 213 received either CLZ 200 mg/d or ticlopidine 500 mg/d or for 6 weeks. One patient died from cerebral infarction after receiving CLZ 200 mg/d for 22 days. Another patient died from acute renal failure after receiving CLZ 200 mg/d for 25 days. The sponsor reports that no serious nonfatal AE were recorded in these trials. In 135 Asian (including Japan) post-marketing studies a total of 2789 patients were exposed to CLZ at doses of 100-300 mg/d for up to 1 year. As of 9/2/96 there were 20 serious AE in 19 patients reported, as follows:

- a. one death in patient S.M, a 72 year old male. No further information was provided.
- b. one event of cardiopulmonary arrest
- c. 2 events of cardiac failure or worsening cardiac failure
- d. one event of myocardial infarction
- e. one event of cerebral infarction
- f. one event of subarachnoid hemorrhage
- g. 3 events of retinal hemorrhage, all occurring on "200 mg"<sup>40</sup> CLZ. One case was patient Y.Y, a 66 year old male; another such event was in patient J.T, a 69 year old male; and the third such AE was in patient N.K, a 42 year old male.
- h. 3 events of melena
- i. one event of Stevens Johnson syndrome
- j. one event of worsened diabetic nephropathy
- k. one event of renal failure
- l. one event of hypoglycemia
- m. one event of sepsis
- n. one event of headache
- o. one case of diarrhea

In a 6 year (1988-1994) uncontrolled Japanese post-marketing surveillance (PMS), 3335 patients were exposed to 50-300 mg/d CLZ. There were 22 reported deaths (all assessed by attending physicians to be not related to the drug), show in the table below by attributed cause, by manufacturer's case number, patient initials, age/sex, dose and treatment duration:

<sup>40</sup> throughout this section of my review I show reported doses in quotation marks when there is uncertainty as to whether they represent total daily doses.

Table: 55

## Reported Deaths in uncontrolled Japanese post-marketing surveillance

<b>Deaths attributed to Heart Failure:</b>				
<b>Death PMS 1:</b> Heart Failure 3A2204 K.K.; 60 yo/M "200 mg" 415 days	<b>Death PMS 2:</b> Heart Failure 3A2314 H.K.; 86/F "200 mg" 31 days	<b>Death PMS 3:</b> Heart Failure 3A2318 F.H.; 82/F "200 mg" 125 days	<b>Death PMS 4:</b> Heart Failure 3A2290 S.A.; 84/M "200 mg" 116 days	<b>Death PMS 5:</b> Heart Failure M.K. 91/F "450" 452 days
<b>Death PMS 6:</b> Heart Failure 2A0857 S.M.; 76/M "150 mg" 50 days	<b>Death PMS 7:</b> Heart Failure 2B0163 K.O.; 96/F "150" 64 days	<b>Death PMS 8: Heart Failure</b> 2A0837 Y.N.; 78/F "200 mg" 83 days	<b>Death PMS 9:</b> Heart Failure 1A0083 T.I. 68/F "200 mg" 40 days	<b>Death PMS 10:</b> Heart Failure 2A0364 S.F. 77/F "200 mg" 45 days
<b>Deaths attributed to MI:</b>				<b>Unattributed causality:</b>
<b>Death PMS 11:</b> 3A1885 Myocardial infarction S.T. 89/F "200 mg" 22 days	<b>Death PMS 12:</b> 3A1645 Myocardial Infarction M.I. 57/M "200 mg" 777 days			<b>Death PMS 22:</b> 3A2197 cause not specified T.K. 84/F "200 mg" 89 days
<b>Deaths attributed to Cerebrovascular diseases:</b>				
<b>Death PMS 13:</b> Cerebral Infarction 2A0522 O.C. 85/M "200 mg" 83 days	<b>Death PMS 14:</b> 2A0594 Cerebral Infarction T.M. 72/M "200 mg" 13 days	<b>Death PMS 15:</b> 2A0333 Subarachnoid Hemorrhage T.T. 64/M "100 mg" 13 days	<b>Death PMS 16:</b> 1B0065 Cerebral Thrombosis S.F. 61/M "200 mg" 112 days	
<b>Deaths attributed to Respiratory diseases:</b>				
<b>Death PMS 17:</b> 2A0762 Acute Respiratory Insufficiency T.F. 72/M "200 mg" 228 days	<b>Death PMS 18:</b> 2A0836 Pneumonia M.A. 81/F "200 mg" 97 days	<b>Death PMS 19:</b> 2A0840 Pneumonia K.S. 78/M "200 mg" 108 days	<b>Death PMS 20:</b> 3A2201 Pneumonia T.T. 72/M "200 mg" 516 days	<b>Death PMS 21:</b> 1A0050 Pneumonia Y.Y. 76/M "200 mg" 10 days

[source: ISS, appendix I, section 1.5]

In this uncontrolled Japanese post-marketing surveillance the most frequently reported AE were headache (3.4%), and palpitation/tachycardia (0.9%). There was one case of severe leukopenia resulting in discontinuation of cilostazol (the reported details are limited to the following: this was patient C.T., a 64 female taking "200 mg" CLZ for 57 days). There was one case of mild thrombocytopenia from which the patient reportedly recovered. There was one case of anemia resulting in with of cilostazol (the reported details are limited to the following: this was patient S.K., a 74 year old male taking "200 mg" CLZ for 85 days). There were 10 reported cases of abnormal hepatic function (including increased SGOT or SGPT).

In Japanese spontaneous post-marketing reports an estimated 725,000 patients have been exposed to CLZ. AE numbering 804 were reported in 581 patients. The serious AE (either meeting FDA criteria or if not strictly meeting FDA criteria, otherwise deemed serious by the attending physician) numbered 133 among 89 patients (rate of 0.018%), and distributed as follows:

Table: 56

**Distribution of serious AE in Japanese spontaneous post-marketing reporting**

<i>body system</i>	<i>fraction of all serious reports</i>
hematologic	18.8%
cardiovascular	15.8%
hepatobiliary	11.2%
respiratory	10.5%
body as a whole	9.0%
gastrointestinal	6.8%
skin	6.8%
urinary	5.3%
cerebrovascular	4.5%
metabolic	3.8%
vision	3.0%
nervous system, nonvascular	2.3%
musculoskeletal	0.8%

[source: ISS, appendix I, section 1.7]

In these Japanese spontaneous post-marketing reports the serious hematologic AE included one case of agranulocytosis, three cases of pancytopenia, thrombocytopenia (n=9), leukopenia (n=8), two cases of hemorrhage, increased bleeding time (n=1), and one case of lymphadenopathy. The serious cardiovascular AE included ventricular tachycardia (n=1), ventricular extrasystole, palpitation, supraventricular tachycardia, tachycardia, cardiac failure, hypotension, and angina.

**11.10 Withdrawal phenomena:**

There are only non-randomized, uncontrolled assessments of post-withdrawal phenomena. The sponsor reports on incidences of cardiovascular AE that started after study drug was stopped. After cessation of drug the number of subsequent MIs were 2, 4, 2, and 1 for cilostazol 50 mg bid, 100 mg bid, 150 mg bid, and placebo, respectively. These observations are subject to potentially important confounding, and thus inherently unable to generate a convincing signal of rebound.

**11.11 Abuse potential:**

Although cilostazol has not been systematically studied in humans for its abuse potential, neither its pharmacologic properties nor clinical trial outcomes suggested any such tendencies.

**12 Overdosage:**

There have been no reported cases of acute overdosage of cilostazol. The sponsor offers the following:

- a. that there is no specific antidote for cilostazol intoxication, but that its treatment ought involve symptomatic and supportive care with respiratory, EKG and blood pressure monitoring.
- b. following acute ingestion the stomach should be emptied immediately, preferably by gastric lavage.
- c. in the event of severe diarrhea, serum electrolyte monitoring and possible hydration with intravenous fluids may be warranted.
- d. dialysis is probably not effective in removing cilostazol because of cilostazol's high (>95%) binding affinity for human plasma albumin.