Original Article

**Efficacy by Ulcer Type and Safety of Lipo-PGE\(_1\) for Japanese Patients with Diabetic Foot Ulcers**

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**Aim:** To examine the efficacy and safety of prostaglandin E\(_1\) incorporated into lipid microspheres (lipo-PGE\(_1\)), Palux\(^\circ\) Injection, in patients with diabetic foot ulcers classified as ischemic, neuropathic, or neuroischemic at 108 medical institutions throughout Japan.

**Methods:** A prospective observational study.

**Results:** The safety and efficacy of the drug were analyzed in 388 and 280 patients, respectively. The overall ulcer size reduction rate at the end of administration was 42.5%: 34.0%, 61.8%, and 33.1% in 71 patients with ischemic ulcer, 70 patients with neuropathic ulcer, and 125 patients with neuroischemic ulcers, respectively. Although lipo-PGE\(_1\) was effective for all the ulcer types examined, the ulcer size reduction rate was significantly higher for neuropathic ulcer than for other types of ulcers. The overall change in the ulcer severity score was -6.1. The change rates in ulcer severity scores were -5.5, -8.4, and -5.2 for ischemic, neuropathic, and neuroischemic ulcers, respectively. The overall efficacy rate was 71.5%. The efficacy rate for neuropathic ulcer was 83.6%, which was significantly higher than for ischemic (68.8%) and neuroischemic (65.3%) ulcers. On the other hand, the incidence of adverse drug reactions was 4.1% (16 cases among 388 patients), indicating that the drug was well tolerated.

**Conclusion:** Lipo-PGE\(_1\) can be administered relatively safely for diabetic foot ulcers and is effective for all the ulcer types examined, especially for neuropathic ulcer.


**Key words:** Lipo-prostaglandin E\(_1\), Diabetic foot ulcer, Post-marketing survey

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**Introduction**

Lipo-prostaglandin E\(_1\) (lipo-PGE\(_1\)), Palux\(^\circ\) Injection, is PGE\(_1\) incorporated into lipid microspheres that are widely used as a nutrient infusion in clinical practice. The lipid microspheres act as drug carriers, presumably contributing to the following characteristic/favorable effects of lipo-PGE\(_1\): its inactivation in the lungs is suppressed because PGE\(_1\) is protected by the lipid microspheres, it has a long duration of action, and it causes fewer adverse drug reactions, e.g., angialgia and phlebitis, since it elicits only slight local irritation at the injection site. Furthermore, the drug has been reported to be superior to conventional PGE\(_1\) preparations because it accumulates in the inflammatory lesion and lesional vessels based on its *in vivo* distribution characteristic of the lipid microspheres\(^1\).

In Japan, the drug is clinically used extensively for indications including 1) extremity ulcers and pain at rest in chronic arterial obstructive disease, 2) skin ulcers in progressive systemic sclerosis and systemic lupus erythematosus, and 3) skin ulcers in diabetes mellitus.

Diabetic foot ulcers present with infection, ulceration, and/or deep tissue destruction in the lower
extremities that involve neurologic abnormalities and different severities of peripheral vascular disease. The ulcers constitute a severe complication of diabetes mellitus that leads to lower extremity amputation if left untreated. Clinically, diabetic foot ulcers are classified into the following types: ischemic; neuropathic; and neuroischemic, a category in which the former two types coexist. It is very important to specify ulcer types in determining the therapeutic option. In two Phase III clinical trials in patients with diabetic neuropathic foot ulcers, the drug was administered for approximately 4 weeks; the efficacy rates of diabetic foot ulcers were 69.0% (20/29 patients) and 81.8% (18/22 patients), respectively; however, no extensive survey on this disorder has been conducted thereafter, or the efficacy of the drug examined by ulcer type.

We conducted the present survey to examine in actual medical practice the efficacy by ulcer type and the safety of the drug for diabetic foot ulcers.

Subjects and Methods

Between June 2004 and July 2007, the present survey was conducted at 108 medical institutions (109 specialties) throughout Japan. The study design was a prospective observational study. Of patients who had diabetic foot ulcers that required administration of the drug, those whose infection at the assessed site was not acute and who did not require surgical debridement of the site during the survey period were subject to the present survey. Patients with necrotic tissue should be included in the study after performing surgical debridement of the site. Administration of the drug was contraindicated for the following patients: patients with serious heart failure, patients with hemorrhage (e.g., intracranial hemorrhage, gastrointestinal bleeding, and hemoptysis), women known or suspected to be pregnant, and patients with a history of hypersensitivity to any ingredient of the drug. Treatment was based on the intravenous bolus injection or intravenous drip infusion of 5 to 10 μg of the drug as alprostadil (lipo-PGE1) once daily. The administration period was generally 4 weeks. Furthermore, since this surveillance was performed in the usual clinical setting, no restriction was applied to any pre-existing combination therapies, e.g., concomitant drugs and surgical treatment.

Diabetic foot ulcers were categorized to the following types by physical examination: ischemic, due to macroangiopathy originating from arteriosclerosis; neuropathic, originating from neuropathy; and neuroischemic, a combination of the two former types (Fig. 1). Physical examination (palpation of foot pulses, i.e., palpation of pulses of the dorsal artery of the foot and posterior tibial artery, and the presence or absence of paresthesia, pain at the ulcer site, intermittent claudication, Achilles reflex, and vibration perception) was performed to determine the causes of diabetic foot ulcers.

Survey items were as follows: patient background factors (gender, age, body mass index (BMI), category of inpatient/outpatient, smoking history, diabetic complications (e.g., diabetic neuropathy, diabetic reti-
Severity scores of diabetic foot ulcers calculated based on DESIGN-R tool items

<table>
<thead>
<tr>
<th>DESIGN-R tool item</th>
<th>Finding</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depth</strong>&lt;br&gt;(measured at the deepest point of the wound)</td>
<td>No particular skin lesion and no redness</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Lesion extends to the dermis</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Lesion extends to subcutaneous tissue</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Lesion extends to muscle, tendon, and bone</td>
<td>15</td>
</tr>
<tr>
<td><strong>Exudate</strong>&lt;br&gt;(frequency of dressing changes)</td>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Slight to moderate</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Heavy</td>
<td>6</td>
</tr>
<tr>
<td><strong>Size</strong>&lt;br&gt;[length (mm) × width (mm)]</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&lt; 400 mm&lt;sup&gt;2&lt;/sup&gt;</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>400 to &lt; 1,600 mm&lt;sup&gt;2&lt;/sup&gt;</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>1,600 to &lt; 3,600 mm&lt;sup&gt;2&lt;/sup&gt;</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>3,600 to &lt; 6,400 mm&lt;sup&gt;2&lt;/sup&gt;</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>6,400 to &lt; 10,000 mm&lt;sup&gt;2&lt;/sup&gt;</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>≥ 10,000 mm&lt;sup&gt;2&lt;/sup&gt;</td>
<td>15</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Obvious signs or local infection</td>
<td>3</td>
</tr>
<tr>
<td><strong>Granulation tissue</strong>&lt;br&gt;(granulation tissue cannot be assessed because the wound is healed or too shallow)</td>
<td>Healthy granulation tissue occupies 50% or more of the lesion</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Healthy granulation tissue occupies less than 50% of the lesion</td>
<td>6</td>
</tr>
<tr>
<td><strong>Necrotic tissue</strong>&lt;br&gt;(necrotic tissue)</td>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>3</td>
</tr>
<tr>
<td><strong>Pocket</strong></td>
<td>Absent</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Present</td>
<td>6</td>
</tr>
</tbody>
</table>

nopathy and diabetic nephropathy), anamnesis, duration of diabetes, and type of diabetes mellitus; history of present illness (duration of foot ulcer, presence or absence of surgical debridement at the site assessed within 1 week prior to the onset of drug administration, and ulcer type); treatment of the disorder (status of drug usage, concomitant drugs, and combination therapies); ulcer condition; improvement of ulcer; ankle brachial pressure index (ABPI); and adverse events.

Ulcer condition was examined with respect to the following aspects and was scored using DESIGN-R (Table 1)<sup>1</sup>–<sup>7</sup>: 1) depth (injury confined to the dermis, injury to subcutaneous tissue, and injury surpassing subcutaneous tissue); 2) exudate (none, slight to moderate: once a day or fewer dressing changes; and heavy: twice a day or more dressing changes); 3) ulcer size [major axis (mm) × minor axis (maximal diameter orthogonal to the major axis, mm)]; 4) presence or absence of local infection signs; 5) healthy granulation tissue [≥50% of the lesion site (including the case in which injury extends to the dermis) and <50% of the lesion site]; 6) presence or absence of necrotic tissue; and 7) presence or absence of pockets.

Table 1. Severity scores of diabetic foot ulcers calculated based on DESIGN-R tool items

1; DESIGN-R represents acronyms derived from the following six items used to classify and assess wound healing progression: “depth”, “exudate”, “size”, “infection”, “granulation”, and “necrotic tissue”.

The medical assessment was conducted at the onset of administration, and 2, 4, and 6 (if any) weeks thereafter, and at the end/discontinuation of administration. Furthermore, in some cases, HbA<sub>1c</sub> was also measured to evaluate diabetes control.

A central committee was established to control the entire survey throughout the procedure, e.g., the unitary of ulcer causes and determination of patient handling,<sup>2</sup> and to evaluate the final outcome of the wound healing efficacy rates.

The efficacy of lipo-PGE<sub>1</sub> administration was evaluated in the following endpoints:

1) Ulcer size reduction rates

The following formula was used to calculate the ulcer reduction rates based on ulcer size:

\[
\text{Ulcerr reduction rate} (\%) = \left(\frac{\text{ulcer size at the onset of administration} - \text{ulcer size at the time of assessment}}{\text{ulcer size at the onset of administration}}\right) \times 100
\]

2) Changes in ulcer severity scores

Ulcer condition was scored according to DESIGN-R in order to determine ulcer severity scores, and its total score was calculated. Furthermore, the following formula was used to determine the change in ulcer severity scores:

\[
\text{Change in ulcer severity scores} = (\text{score at the time of assessment}) - (\text{score at the onset of administration})
\]

3) Efficacy rates for diabetic foot ulcers

At the end/discontinuation of administration, the attending physician determined the efficacy of the drug for diabetic foot ulcers according to the following 5-category criterion: “markedly improved”, “improved”, “slightly improved”, “unchanged”, “deteriorated”, and “indeterminable”. Furthermore, the following formula was used to calculate efficacy rates:

\[
\text{Efficacy rate} (\%) = \left(\frac{\text{number of “effective” patients}}{\text{number of “effective” patients} + \text{number of “ineffective” patients}}\right) \times 100
\]

Number of “effective” patients: number of “mark-
edly improved” and “improved” patients

Number of “ineffective” patients: number of “slightly improved”, “unchanged”, and “deteriorated” patients

4) Changes in ABPI

The following formula was used to calculate changes in ABPI:

Changes in ABPI: [ABPI at the end/discontinuation of administration−(ABPI at the onset of administration)]

Statistical Analysis

The Clinical Works 4/CDM database (R-2.2; Hewlett-Packard Japan, Ltd., Tokyo, Japan) was used for the entry and validation/verification of data. Furthermore, SAS (ver. 9.1, SAS Institute Japan Ltd., Tokyo, Japan) at Taisho Pharmaceutical Co., Ltd. was used to analyze the data. Unless otherwise specified, statistical analyses were performed by the two-tailed Student’s t-test or χ² test (p<0.05), and for multiple comparisons, post-hoc group comparisons were performed by means of Bonferroni’s correction.

Results

Case Handling

The present survey enrolled 409 patients, and case report forms were collected from 392 patients. Of them, drug safety was analyzed in 388 patients after excluding 4 patients (3 who were enrolled after the onset of administration and 1 who was re-enrolled after his first enrollment). Efficacy was analyzed in 280 patients after excluding the following 108 patients from those analyzed for safety: 10 who had diseases other than diabetic foot ulcers; 33 whose ulcer size before or after administration was not measured; 33 to whom the drug was discontinued for reasons other than healing/improvement or inefficacy/deterioration prior to day 21 of administration; 18 who underwent surgical debridement during the administration period of the drug and whose ulcer size prior to debridement was not measured; 6 whose ulcer size on day 21 and subsequent days of administration was not measured; 4 who had a ≥8-day withdrawal period and whose administration period prior to drug withdrawal lasted for less than 21 days; 2 whose ulcer size during the survey period was not measured; and 2 who underwent surgery at the assessed site and whose ulcer size prior to surgery was not measured.

Patient Background Factors in the Efficacy-Evaluated Population

The numbers of patients by ulcer type were as follows: 71 patients (25.4%) for ischemic ulcer, 70 patients (25.0%) for neuropathic ulcer, 125 patients (44.6%) for neuroischemic ulcer, and 14 patients (5.0%) for uncategorizable ulcer; therefore, neuroischemic ulcer was the most predominant. Patient background factors analyzed for efficacy after excluding 14 patients with uncategorizable ulcer are shown in Table 2. Patient background factors showing bias among the 3 survey groups by ulcer type at a significance level of <0.05 were age, category of inpatient/outpatient, complications, duration of diabetes, type of diabetes mellitus, and ABPI at the onset of administration. Furthermore, three patients had a history of revascularization of the lower extremities, and seven patients underwent revascularization during the administration period of the drug. Of these patients, five were excluded from the analysis of efficacy due to other reasons. Therefore, efficacy in two patients was assessed with data that had been obtained prior to revascularization.

Changes in Reduction Rates and Sizes of Diabetic Foot Ulcers

Time-course changes in the reduction rates and sizes of diabetic foot ulcers are shown in Fig. 2 and 3, respectively. The overall ulcer size reduction rate at the end/discontinuation of administration was 42.5 ± 3.4% (mean ± SE). The ulcer reduction rates by ulcer type were 34.0 ± 7.7%, 61.8 ± 4.0%, and 33.1 ± 5.6% for ischemic, neuropathic, and neuroischemic types, respectively. The reduction rate was significantly higher for neuropathic ulcer than for neuroischemic ulcers (neuropathic vs. neuroischemic; p<0.005). The reduction rate in 14 patients with uncategorizable ulcer was 72.6 ± 8.8%. Regarding the time-course changes in ulcer reduction rates by ulcer type, all ulcer types examined showed increases in the rates on a time-course basis, i.e., at weeks 2, 4, and 6 of administration (p<0.05). Ulcer size at the onset of administration was largest for neuropathic ulcer. Ulcer size reduced in all ulcer types examined on a time-course basis. Ulcer size at the end of administration was smallest for neuropathic ulcer.

The covariate adjustment method was performed using the following patient background factors as covariates: those showing bias among the 3 study groups by ulcer type at a significance level of <0.05 were age, category of inpatient/outpatient, complications, duration of diabetes, type of diabetes mellitus, and ABPI at the onset of administration. The reduction rate of neuropathic ulcer was high for the covariates.
Table 2. Patient background factors analyzed for efficacy

<table>
<thead>
<tr>
<th></th>
<th>Ischemic (n=71)</th>
<th>Neuropathic (n=70)</th>
<th>Neuroischemic (n=125)</th>
<th>p value (χ² test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45 63.4</td>
<td>49 70.0</td>
<td>85 68.0</td>
<td>0.685</td>
</tr>
<tr>
<td>Female</td>
<td>26 36.6</td>
<td>21 30.0</td>
<td>40 32.0</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&lt; 15</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>0 0.0</td>
<td>0.002</td>
</tr>
<tr>
<td>≥ 15</td>
<td>26 36.6</td>
<td>44 62.9</td>
<td>49 39.2</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>66.1 ± 11.8</td>
<td>60.3 ± 13.5</td>
<td>67.9 ± 11.4</td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 18.5</td>
<td>5 7.4</td>
<td>8 12.1</td>
<td>19 16.0</td>
<td>0.130</td>
</tr>
<tr>
<td>≥ 18.5</td>
<td>48 70.6</td>
<td>34 51.5</td>
<td>75 63.0</td>
<td></td>
</tr>
<tr>
<td>≥ 25</td>
<td>13 19.1</td>
<td>19 28.8</td>
<td>22 18.5</td>
<td></td>
</tr>
<tr>
<td>≥ 30</td>
<td>2 2.9</td>
<td>5 7.6</td>
<td>3 2.5</td>
<td></td>
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<tr>
<td>Unknown</td>
<td>0 0</td>
<td>4 4</td>
<td>6 5</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>13.4 ± 2.3</td>
<td>15.1 ± 2.6</td>
<td>17.4 ± 2.6</td>
<td></td>
</tr>
<tr>
<td>Category of outpatient/inpatient</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient</td>
<td>22 31.0</td>
<td>15 21.7</td>
<td>18 14.4</td>
<td>0.009</td>
</tr>
<tr>
<td>Inpatient</td>
<td>41 57.7</td>
<td>53 76.8</td>
<td>95 76.0</td>
<td></td>
</tr>
<tr>
<td>Unspecified</td>
<td>8 11.3</td>
<td>1 1.4</td>
<td>12 9.6</td>
<td>0.80</td>
</tr>
<tr>
<td>Smoking Status</td>
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<tr>
<td>Present (current)</td>
<td>11 15.7</td>
<td>14 20.6</td>
<td>6 21.3</td>
<td>0.110</td>
</tr>
<tr>
<td>Present (past)</td>
<td>16 22.9</td>
<td>18 26.5</td>
<td>31 25.4</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>43 61.4</td>
<td>36 52.9</td>
<td>65 53.3</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1 0</td>
<td>2 0</td>
<td>3 0</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>13.4 ± 2.3</td>
<td>15.1 ± 2.6</td>
<td>17.4 ± 2.6</td>
<td></td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>12 16.9</td>
<td>6 8.6</td>
<td>2 1.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetic complications Present</td>
<td>48 67.6</td>
<td>61 87.1</td>
<td>122 97.6</td>
<td></td>
</tr>
<tr>
<td>Diabetic complications Absent</td>
<td>11 15.5</td>
<td>3 4.3</td>
<td>1 0.8</td>
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</tr>
<tr>
<td>Duration of diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 10 years</td>
<td>28 45.9</td>
<td>29 42.0</td>
<td>24 22.0</td>
<td>0.002</td>
</tr>
<tr>
<td>≥ 10 years</td>
<td>33 54.1</td>
<td>40 58.0</td>
<td>85 78.0</td>
<td></td>
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<tr>
<td>Unknown</td>
<td>10 14.3</td>
<td>1 1.4</td>
<td>16 13.4</td>
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</tr>
<tr>
<td>Mean ± SD</td>
<td>13.4 ± 2.3</td>
<td>15.1 ± 2.6</td>
<td>17.4 ± 2.6</td>
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</tr>
<tr>
<td>Type of diabetes mellitus</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>12 16.9</td>
<td>7 10.8</td>
<td>4 3.2</td>
<td>0.002</td>
</tr>
<tr>
<td>Type 2</td>
<td>57 80.3</td>
<td>62 88.6</td>
<td>119 95.2</td>
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<tr>
<td>Unclassified</td>
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<td>1 1.4</td>
<td>2 1.6</td>
<td></td>
</tr>
<tr>
<td>Duration of ulcer (months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1</td>
<td>26 37.1</td>
<td>26 37.1</td>
<td>39 31.5</td>
<td>0.002</td>
</tr>
<tr>
<td>≥ 1</td>
<td>18 25.7</td>
<td>24 34.3</td>
<td>38 30.6</td>
<td></td>
</tr>
<tr>
<td>≥ 2</td>
<td>26 37.1</td>
<td>20 28.6</td>
<td>47 37.9</td>
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<td>Unknown</td>
<td>1 1.4</td>
<td>0 0</td>
<td>1 1</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>190.1 ± 77.5</td>
<td>76.4 ± 137.7</td>
<td>98.3 ± 169.6</td>
<td></td>
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<tr>
<td>Debridement before administration</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Absent</td>
<td>47 66.2</td>
<td>49 70.0</td>
<td>86 68.8</td>
<td>0.882</td>
</tr>
<tr>
<td>Present</td>
<td>24 33.8</td>
<td>21 30.0</td>
<td>39 31.2</td>
<td></td>
</tr>
<tr>
<td>Ulcer size (mm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 100</td>
<td>20 28.2</td>
<td>11 15.7</td>
<td>27 21.6</td>
<td>0.548</td>
</tr>
<tr>
<td>≥ 100</td>
<td>11 15.5</td>
<td>7 10.0</td>
<td>22 17.6</td>
<td></td>
</tr>
<tr>
<td>≥ 200</td>
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<td>6 8.6</td>
<td>21 16.8</td>
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<td>≥ 300</td>
<td>5 7.0</td>
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</tr>
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<td>≥ 400</td>
<td>8 11.3</td>
<td>15 21.4</td>
<td>20 16.0</td>
<td></td>
</tr>
<tr>
<td>≥ 600</td>
<td>5 7.0</td>
<td>6 8.6</td>
<td>9 7.2</td>
<td>0.344</td>
</tr>
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<td>3 4.2</td>
<td>6 8.6</td>
<td>6 4.8</td>
<td></td>
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<tr>
<td>≥ 1600</td>
<td>5 7.0</td>
<td>9 12.9</td>
<td>11 8.4</td>
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</tr>
<tr>
<td>≥ 3600</td>
<td>4 5.6</td>
<td>4 5.7</td>
<td>5 4.0</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>91.5 ± 22.84</td>
<td>2.158 ± 3.284</td>
<td>787.6 ± 165.2</td>
<td></td>
</tr>
<tr>
<td>Severity scores for diabetic foot ulcers at the onset of treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–10</td>
<td>9 12.7</td>
<td>8 11.4</td>
<td>11 8.9</td>
<td></td>
</tr>
<tr>
<td>11–15</td>
<td>36 50.7</td>
<td>24 34.3</td>
<td>53 42.7</td>
<td></td>
</tr>
<tr>
<td>16–20</td>
<td>13 18.3</td>
<td>17 24.3</td>
<td>35 28.2</td>
<td></td>
</tr>
<tr>
<td>21–30</td>
<td>12 16.9</td>
<td>21 30.0</td>
<td>24 19.4</td>
<td></td>
</tr>
<tr>
<td>≥ 31</td>
<td>1 1.4</td>
<td>0 0</td>
<td>1 0.8</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>0 0</td>
<td>0 0</td>
<td>1 1</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>16.0 ± 2.8</td>
<td>17.1 ± 2.6</td>
<td>16.7 ± 4.7</td>
<td></td>
</tr>
<tr>
<td>ABPI at the onset of treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 0.4</td>
<td>1 2.8</td>
<td>0 0</td>
<td>2 4.3</td>
<td></td>
</tr>
<tr>
<td>≤ 0.9</td>
<td>12 33.5</td>
<td>2 3.2</td>
<td>23 50.0</td>
<td></td>
</tr>
<tr>
<td>≤ 1.3</td>
<td>23 63.9</td>
<td>20 53.3</td>
<td>20 43.5</td>
<td></td>
</tr>
<tr>
<td>&gt; 1.3</td>
<td>0 0</td>
<td>2 3.2</td>
<td>1 2.2</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>26 73.7</td>
<td>65 65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>0.96 ± 0.21</td>
<td>0.10 ± 0.15</td>
<td>0.89 ± 0.26</td>
<td></td>
</tr>
<tr>
<td>Treatment duration (days)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>32.2 ± 17.2</td>
<td>30.3 ± 18.9</td>
<td>31.5 ± 23.2</td>
<td></td>
</tr>
</tbody>
</table>

Underlining indicates p < 0.05. The “Unknown” subcategory was excluded from the analysis.
Changes in Ulcer Severity Scores

The overall change in ulcer severity scores at the end/discontinuation of administration was \(-6.1 \pm 0.4\) (mean \(\pm\) SE). Changes in severity scores in each ulcer type were \(-5.5 \pm 0.8\), \(-8.4 \pm 0.8\), and \(-5.2 \pm 0.6\) for ischemic, neuropathic, and neuroischemic ulcers, respectively, in which the greatest reduction in severity score was observed in neuropathic ulcers, but with no significant difference from the other two groups. Furthermore, all ulcer types examined showed large time-course changes; however, the change at week 4 of administration was significantly smaller for neuroischemic ulcer than for neuropathic ulcer (Fig. 4). The scores for all ulcer types fell over time. The ulcer severity score at the end of administration was lowest for neuropathic ulcer (Fig. 5).

Changes in severity scores by ulcer type at the end/discontinuation of administration are shown in Table 3. The change for neuropathic ulcer was large in most survey items.

Efficacy Rates for Diabetic Foot Ulcers

Efficacy rates in patients who were assessed as “effective” by the attending physician at the end/discontinuation of administration are shown in Fig. 6. The overall efficacy rate was 71.5% (188/263 patients); 17 “indeterminable” patients were excluded from 280 patients analyzed for efficacy. The efficacy rates by ulcer type were 68.8% (44/64 patients), 83.6% (56/67 patients), and 65.3% (77/118 patients) for ischemic, neuropathic, and neuroischemic ulcers, respectively; therefore, the efficacy rate was significantly higher for neuropathic ulcer than for ischemic and neuroischemic ulcers (\(p<0.05\) and \(p<0.01\), respectively).

Changes in ABPI

ABPI were evaluated in 53 patients before and after administration, and changes in ABPI were calculated (Table 4). The mean change in ABPI for all patients was as low as 0.038 and showed no difference among ulcer types.

Drug Safety

In the present survey, 16 cases (20 events) of adverse drug reactions were observed in 388 patients who were analyzed for safety. The incidence of adverse drug reactions was 4.1%. Of them, there were 4 cases...
(4 events) of serious adverse drug reactions, i.e., 1 case of gastric hemorrhage, 1 case of pleural effusion, and 2 cases of congestive cardiac failure. The list of reported adverse drug reactions is shown in Table 5.

Discussion

According to “the 2005 Survey on Patients” published by the Ministry of Health, Labor and Welfare, there were approximately 2.47 million patients with diabetes mellitus as of that year. The number of diabetic patients increased slightly by 13% as compared with the 1996 Survey value of approximately 2.18 million patients.

Foot ulcers in diabetic patients are a major health problem and have a prevalence of 4 to 10% in the diabetic population. Medical costs for diabetic ulcers were estimated to be US$18,000 to 34,000 per patient in a 1999 US study and a 2000 Swedish study.

Clinically, therapeutic options differ among ischemic, neuropathic, and neuroischemic types. The main therapeutic measures are revascularization and pharmacotherapy with vasodilators for ischemic ulcers, and the therapeutic approaches common to all types of diabetic ulcers include relief of mechanical stress, metabolic control, management of infection, edema, and pain, as well as topical treatment.

Mechanical stress, reduced blood flow, reduced skin oxygenation, and autonomic neuropathy are involved in the pathogenesis of neuropathic diabetic ulcers and interact with the microcirculation, resulting in the failure of skin capillary flow.

To examine the efficacy and safety of the drug for diabetic foot ulcers, two Phase III clinical trials were previously conducted in Japanese patients who had diabetic neuropathic foot ulcers. Consequently, high efficacy and safety rates of the drug for neuropathic foot ulcers were found; however, its efficacy and safety for two other types of diabetic foot ulcers (i.e., ischemic and neuroischemic ulcers) remained unknown. Therefore, we conducted the present survey...
Table 3. Severity scores of diabetic foot ulcers

<table>
<thead>
<tr>
<th>DESIGN-R tool item</th>
<th>Ulcer type</th>
<th>Pretreatment</th>
<th>Post-treatment</th>
<th>ΔScore</th>
<th>p value (Bonferroni)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
<td>Mean</td>
<td>SE</td>
<td>N</td>
</tr>
<tr>
<td>Exudate (frequency of dressing changes)</td>
<td>Total</td>
<td>279</td>
<td>3.4</td>
<td>1</td>
<td>280</td>
</tr>
<tr>
<td></td>
<td>Ischemic</td>
<td>71</td>
<td>3.3</td>
<td>1</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>Neuropathic</td>
<td>70</td>
<td>3.4</td>
<td>1</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Neuroischemic</td>
<td>124</td>
<td>3.5</td>
<td>1</td>
<td>125</td>
</tr>
<tr>
<td>Ulcer size [length (mm) × width (mm)]</td>
<td>Total</td>
<td>280</td>
<td>4.7</td>
<td>0.1</td>
<td>280</td>
</tr>
<tr>
<td></td>
<td>Ischemic</td>
<td>71</td>
<td>4.5</td>
<td>0.3</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>Neuropathic</td>
<td>70</td>
<td>5.2</td>
<td>0.3</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Neuroischemic</td>
<td>125</td>
<td>4.6</td>
<td>0.2</td>
<td>125</td>
</tr>
<tr>
<td>Infection</td>
<td>Total</td>
<td>280</td>
<td>0.9</td>
<td>0.1</td>
<td>278</td>
</tr>
<tr>
<td></td>
<td>Ischemic</td>
<td>71</td>
<td>1.0</td>
<td>0.2</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>Neuropathic</td>
<td>70</td>
<td>0.9</td>
<td>0.2</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>Neuroischemic</td>
<td>125</td>
<td>0.9</td>
<td>0.1</td>
<td>124</td>
</tr>
<tr>
<td>Granulation tissue</td>
<td>Total</td>
<td>280</td>
<td>4.9</td>
<td>0.1</td>
<td>279</td>
</tr>
<tr>
<td></td>
<td>Ischemic</td>
<td>71</td>
<td>5.1</td>
<td>0.2</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>Neuropathic</td>
<td>70</td>
<td>4.8</td>
<td>0.2</td>
<td>69</td>
</tr>
<tr>
<td></td>
<td>Neuroischemic</td>
<td>125</td>
<td>5.0</td>
<td>0.1</td>
<td>125</td>
</tr>
<tr>
<td>Necrotic tissue</td>
<td>Total</td>
<td>280</td>
<td>1.7</td>
<td>0.1</td>
<td>280</td>
</tr>
<tr>
<td></td>
<td>Ischemic</td>
<td>71</td>
<td>1.6</td>
<td>0.2</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>Neuropathic</td>
<td>70</td>
<td>1.6</td>
<td>0.2</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Neuroischemic</td>
<td>125</td>
<td>1.8</td>
<td>0.1</td>
<td>125</td>
</tr>
<tr>
<td>Pocket</td>
<td>Total</td>
<td>280</td>
<td>0.9</td>
<td>0.1</td>
<td>280</td>
</tr>
<tr>
<td></td>
<td>Ischemic</td>
<td>71</td>
<td>0.6</td>
<td>0.2</td>
<td>71</td>
</tr>
<tr>
<td></td>
<td>Neuropathic</td>
<td>70</td>
<td>1.1</td>
<td>0.3</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>Neuroischemic</td>
<td>125</td>
<td>1.0</td>
<td>0.2</td>
<td>125</td>
</tr>
</tbody>
</table>

Fig. 6. Efficacy rates for diabetic foot ulcers at the end of administration.

Categories of efficacy: “markedly improved”, “improved”, “slightly improved”, “unchanged”, and “deteriorated”
The efficacy rate in 14 patients with uncategorizable ulcer was 78.6% (11/14 patients) and is not shown in the figure.
to examine its therapeutic effects and safety for patients with one of these three ulcer types in actual medical practice.

The present observational survey provided the following facts: 1) the efficacy rates of the drug for neuropathic foot ulcers were not inferior to those from the two previous Phase III clinical trials of the drug, although they cannot be compared directly; 2) the drug showed high ulcer reduction rates, efficacy rates, and changes in severity scores for all three diabetic ulcer types examined; and 3) the drug was significantly more effective for neuropathic foot ulcer than for ischemic and neuroischemic ulcers.

Two major mechanisms have been proposed as pathogenic factors for diabetic neuropathies: metabolic disturbance by which the metabolic cascade, including hypermetabolism of polyol, glycation, oxidative stress, altered activity of protein kinase C, and altered activity of poly-ADP-ribose polymerase (PARP), leads to the impairment of peripheral nervous tissue and provokes neurodegeneration; and the secondary mechanism by which microvessels nourishing nervous tissue cause nerve lesions attributed to ischemia-reperfusion injury induced by microangiopathy.

The drug is considered to exert its pharmacological effects on diabetic foot ulcers through 1) peripheral blood flow-increasing activity based on its vasodilating action, 2) improvement of the peripheral circulation due to its platelet aggregation-inhibitory action, and 3) enhancement of neovascularization of granulation tissue.

Yamaguchi et al. and Ozeki et al., respectively, have reported the following pharmacological actions of PGE1: improvement of erythrocyte deform-

Table 4. Ankle brachial pressure indexes at baseline and end of administration (EOA), as well as their changes from baseline

<table>
<thead>
<tr>
<th>Ulcer type</th>
<th>N</th>
<th>ABPI (Mean ± SE)</th>
<th>Δ</th>
<th>SE</th>
<th>Min</th>
<th>Median</th>
<th>Max</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline</td>
<td>EOA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>53</td>
<td>0.93 ± 0.04</td>
<td>0.97 ± 0.03</td>
<td>0.038</td>
<td>0.02</td>
<td>-0.20</td>
<td>0.00</td>
<td>0.74</td>
</tr>
<tr>
<td>Ischemic</td>
<td>18</td>
<td>0.96 ± 0.06</td>
<td>0.99 ± 0.05</td>
<td>0.028</td>
<td>0.02</td>
<td>-0.15</td>
<td>0.01</td>
<td>0.30</td>
</tr>
<tr>
<td>Neuropathic</td>
<td>11</td>
<td>1.06 ± 0.06</td>
<td>1.10 ± 0.06</td>
<td>0.041</td>
<td>0.07</td>
<td>-0.10</td>
<td>0.01</td>
<td>0.74</td>
</tr>
<tr>
<td>Neuroischemic</td>
<td>23</td>
<td>0.84 ± 0.06</td>
<td>0.89 ± 0.05</td>
<td>0.045</td>
<td>0.02</td>
<td>-0.20</td>
<td>0.01</td>
<td>0.28</td>
</tr>
</tbody>
</table>

Δ: Mean change from baseline, CI: confidence interval

Table 5. Adverse drug reactions

<table>
<thead>
<tr>
<th>System organ class (SOC)</th>
<th>Preferred term (PT)</th>
<th>Number of adverse events</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Gastric hemorrhage</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Hepatic function abnormal</td>
<td>4</td>
<td>1.0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Vasculitis</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Phlebitis</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Effusion pleural</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Respiratory disorder</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Cardiac failure congestive</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Cardiac failure acute</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Cardiac failure</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Palpitations</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Hypoaesthesia</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Pruritus</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>Erythema</td>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>Investigations</td>
<td>Eosinophil count increased</td>
<td>1</td>
<td>0.3</td>
</tr>
</tbody>
</table>

1: Terminology is from the Medical Dictionary for Regulatory Activities (MedDRA/J Ver. 11.0).
ability, which is decreased in chronic arterial obstructive disease; and improvement of leukocyte filterability, which is considered a microcirculation-deteriorating factor under ischemic conditions. Furthermore, PGE\(_1\) has been reported to have the following new pharmacological actions\(^20,21\): improvement of decreased plasma concentrations of VCAM-1 in patients with arteriosclerosis obliterans; improvement of decreased plasma concentrations of ICAM-1; improvement of decreased serum concentrations of MCP-1; and improvement of flow-mediated dilation (FMV), a variable for vascular endothelial function.

On the other hand, enhancement of the inflammatory response and decreased function of vascular endothelium, apart from changes in hemorheology and activation of platelets, were recently estimated to play important roles in the mechanism of severe ischemia of the lower extremities\(^22\); therefore, PGE\(_1\) possibly improves local adverse conditions and the associated vicious cycle by exerting not only vasodilating activity and platelet aggregation-inhibitory activity, but also hemorheology-improving activity, anti-inflammatory activity, and vascular endothelial function-improving activity.

Prior to the present survey, we envisaged that no significant difference would be found in the efficacy rates of the drug for three types of diabetic foot ulcers; however, the drug showed significantly higher efficacy rates for neuropathic ulcer. We presume that this result was possibly attributed to the following facts: 1) microcirculation impairments occurred mainly in neuropathic diabetic foot ulcers, while both macro- and microcirculation impairments occurred mainly in ischemic and neuroischemic ulcers; and 2) the drug showed equivalent pharmacological actions on all types, which resulted in the apparently greater improvement of the neuropathic type. The drug improved both macro- and microcirculations, which led to the relatively greater improvement of the latter. We presume that this improvement was reflected in the better efficacy rates of the drug for neuropathic diabetic ulcers.

Analysis of the changes in severity scores in the present survey revealed the following facts: necrotic tissue in an ischemic ulcer is less prone to be removed by skin care and other means; and healthy granulation tissue proliferates slowly in neuroischemic ulcer. We considered that blood flow disturbance is greatly involved in the lower tendency to heal of “necrotic tissue” and “granulation tissue” in ischemic and neuroischemic ulcers than in neuropathic ulcer. We deemed that the ulcer severity score is a useful variable to comprehend the ulcer condition in individual patients, apart from ulcer size.

ABPI was measured in a limited number of patients in the present study, which made the influences of ABPI on therapeutic effects by ulcer type unclear; however, examination of the ulcer reduction rates adjusted with ABPI, which was used as a covariate, indicated reduced differences in the rates among ulcer types. Therefore, macrocirculation in the lower extremities was suggested to be one of the factors affecting the therapeutic effects of the drug.

The incidence of adverse drug reactions in the present survey was almost equivalent to the average in previous post-marketing surveys on the indications of the drug in adults, 3.70% (472 cases among 12,747 patients).

A limitation of this study is that it is a post-marketing survey. Since the survey was conducted in the usual clinical setting on a large scale (108 medical institutions throughout Japan) to examine efficacy by ulcer type and the safety of lipo-PGE\(_1\) in patients with diabetic foot ulcers, diabetic foot ulcers were categorized according to the widely-used standard diagnostic criteria\(^2,3\) and no restriction was applied to pre-existing therapeutic regimens, e.g., concomitant drugs and endovascular therapy.

**Conclusions**

In 1995, the clinical indication of “improvement of foot ulcers in diabetes mellitus” was approved additionally for lipo-PGE\(_1\) (Palux\(^\circledast\) Injection); however, the efficacy of the drug by ulcer type for this disorder has not been examined thereafter. Hence, we conducted the present survey to examine the efficacy by ulcer type and the safety of the drug for diabetic foot ulcers in actual medical practice. We obtained the following conclusions:

1) The overall ulcer size reduction rate at the end/discontinuation of administration was 42.5%. The reduction rates by ulcer type were 34.0%, 61.8%, and 53.1% for ischemic, neuropathic, and neuroischemic ulcers, respectively; therefore, the drug showed efficacy for all ulcer types. The rate was significantly higher for neuropathic ulcer than for other ulcer types.

2) The overall change in ulcer severity scores (DESIGN-R) at the end/discontinuation of administration was -6.1. The changes by ulcer type were -5.5, -8.4, and -5.2 for ischemic, neuropathic, and neuroischemic ulcers, respectively.

3) The overall efficacy rate at the end/discontinuation of administration was 71.5%. The efficacy rates by ulcer type were 68.8%, 83.6%, and 65.3% for ischemic, neuropathic, and neuroischemic ulcers,
respectively. The rate was significantly higher for neuropathic ulcer than for other ulcer types.

4) The incidence of adverse drug reactions was 4.1% (16 cases among 388 patients), revealing that the drug was well tolerated.

Based on the above results, we consider that the drug can be administered relatively safely for diabetic foot ulcers without acute infection and is an effective therapeutic measure for all the ulcer types examined. The drug was effective, especially for neuropathic ulcer.

Acknowledgments

The authors are very grateful to the investigators at the 108 medical institutions throughout Japan for their cooperation in conducting the present survey.

Medical institutions that cooperated with the present survey: Asahikawa Red-Cross Hospital, Hokkaido Chuo Rosai Hospital, National Hospital Organization Hakodate Hospital, Sapporo Midori-no Clinic, National Hospital Organization Nishi Sapporo National Hospital, Sapporo Satozuka Hospital, Aomori Prefectural Central Hospital, Kuroishi General Hospital, Japanese Red Cross Sendai Hospital, Yamamoto Kumiai General Hospital, Seihuukai Seiwa Hospital, Takeda General Hospital, Jusendo General Hospital, Ohta Nishinouchi Hospital, Shirakawa Kosei General Hospital, Tokyo Medical University Ibaraki Medical Center, Tsukuba University Hospital, Gunma University Hospital, Kasukabe Municipal Hospital, Fukushima Hospital, National Hospital Organization Nishisaitama-Chuo National Hospital, Dokkyo Medical University Koshigaya Hospital, National Medical Organization Chiba Medical Center, Chiba University Hospital, Tokyo Dental College Ichikawa General Hospital, Shin-Tokyo Hospital, Tokyo Women's Medical University Medical Center East, Asoka Hospital, Kanto Medical Center NTT EC, Japanese Red Cross Medical Center, Tokyo Kosei Nenkin Hospital, Tokyo Medical University Hospital, The Fraternity Memorial Hospital, Kudanakazi Hospital, Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital, Tokyo Takanawa Hospital, Toho University Ohashi Medical Center, National Hospital Organization Disaster Medical Center, Yokohama Social Insurance Chuo Hospital, Kitasato University Hospital, Fujisawa City Hospital, Yokosuka Kyosai Hospital, St. Marianna University School of Medicine Hospital, Nippon Medical School Musashi Kosugi Hospital, Saiseikai Yokohamashi Nanbu Hospital, Yokohama City Seibu Hospital, St. Marianna University School of Medicine, National Hospital Organization Yokohama Medical Center, Saiseikai Takaoka Hospital, Kanazawa University Hospital, Ishikawa Prefectural Central Hospital, Komatsu Municipal Hospital, Okayama Enrei Hospital, National Hospital Organization Matsumoto Medical Center, Yodakubo Hospital, Gifu Municipal Hospital, Gifu Prefectural Tajimi Hospital, Shizuoka City Shimizu Hospital, Nagoya University Hospital, National Hospital Organization Nagoya Medical Center, Tosei General Hospital, Toyokawa City Hospital, Fuji Health University Hospital, Aichi Medical University, Chita City Hospital, Otsu Red Cross Hospital, Naga-hama Red Cross Hospital, Uchida Hospital, Saikyo Hospital, Kyoto University Graduate School of Medicine, Kyoto City Hospital, Dai-ni Okamoto General Hospital, Osaka General Medical Center, NTT West Osaka Hospital, Osaka Koseinenkin Hospital, Osaka City Sumiyoshi Hospital, Sakai Municipal Hospital, Yao Municipal Hospital, Kinki University School of Medicine, National Hospital Organization Osaka Medical Center, Kobe City Hospital Organization Medical Center West Hospital, Kobe University Hospital, Kinki Central Hospital, Ono Municipal Hospital, Kobe City Hospital Organization Kobe City Medical Center General Hospital, Nara Prefectural Gojo Hospital, Tenri Hospital, Oyodo Municipal Hospital, Kurashiki Central Hospital, JA Onomichi General Hospital, National Hospital Organization Higashi Hiroshima Medical Center, Hiroshima City Hospital, Ube Kyoritsu Hospital, Tokushima University Hospital, Omuta City General Hospital, Kitakyushu City Yahata Hospital, Kurume University Hospital, Saiseikai Fukuoka General Hospital, Hamanomachi Hospital, Chikugogawa Onsen Hospital, Munakata Suiko- kai General Hospital, National Hospital Organization Kyushu Medical Center, Izumikawa Hospital, Health Insurance Hitoyoshi General Hospital, Nishinichon Hospital, Oita Oka Hospital, National Hospital Organization Beppu Medical Center, Social Insurance Miyazaki Konan Hospital, and University of the Ryukyus

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