Report on the Deliberation Results

December 4, 2019

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Orkedia Tablets 1 mg Orkedia Tablets 2 mg
Non-proprietary Name	Evocalcet (JAN*)
Applicant	Kyowa Kirin Co., Ltd.
Date of Application	April 24, 2019

Results of Deliberation

In its meeting held on November 29, 2019, the First Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 10 years.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.

2. Since only a limited number of patients participated in clinical studies of the product in Japan, the applicant is required to conduct a post-marketing drug use-results survey involving all patients treated with the product until data from a specified number of patients have been gathered in order to understand the characteristics of patients treated with the product, and to collect safety and efficacy data as early as possible, so that necessary measures are taken to ensure proper use of the product.

**Japanese Accepted Name (modified INN)*

Review Report

November 11, 2019
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Orkedia Tablets 1 mg Orkedia Tablets 2 mg
Non-proprietary Name	Evocalcet
Applicant	Kyowa Kirin Co., Ltd. (formerly Kyowa Hakko Kirin Co., Ltd.)
Date of Application	April 24, 2019
Dosage Form/Strength	Film-coated tablets: Each tablet contains 1 or 2 mg of Evocalcet.
Application Classification	Prescription drug, (4) Drug with new indications and (6) Drug with new dosages
Items Warranting Special Mention	Orphan drug (Orphan Drug Designation No. 426 of 2019 [*31 yaku*]; PSEHB/PED Notification No. 0304-1 dated March 4, 2019, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug I

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of "hypercalcaemia in patients with parathyroid carcinoma and hypercalcaemia in patients with primary hyperparathyroidism who are unable to undergo parathyroidectomy or patients with recurrent primary hyperparathyroidism after parathyroidectomy," and that the product has acceptable safety in view of its benefits (see Attachment). The safety and efficacy of the product should be further investigated in the post-marketing surveillance covering all patients who used the product for the treatment of hypercalcaemia associated with parathyroid carcinoma or hypercalcaemia associated with primary hyperparathyroidism unable to be treated by parathyroidectomy or with recurrent primary hyperparathyroidism after parathyroidectomy.

As a result of its review, PMDA has concluded that the product may be approved for the indications and dosage and administration shown below, with the following conditions.

Indications

○ Secondary hyperparathyroidism in patients on maintenance dialysis

○ Hypercalcaemia in patients with any of the following conditions:

- Parathyroid carcinoma
- Primary hyperparathyroidism unable to be treated by parathyroidectomy or recurrent primary hyperparathyroidism after parathyroidectomy

(Underline denotes additions.)

Dosage and Administration

Secondary hyperparathyroidism in patients on maintenance dialysis:

The usual starting dosage for adults is 1 mg of evocalcet administered orally once daily. The starting dose may be 2 mg once daily, depending on the patient's condition. The subsequent oral dose is adjusted within the range from 1 to 8 mg once daily while parathyroid hormone (PTH) and serum calcium levels of the patient are closely monitored. The dose may be increased up to 12 mg once daily if the patient has an inadequate response.

Hypercalcaemia in patients with parathyroid carcinoma and hypercalcaemia in patients with primary hyperparathyroidism who are unable to undergo parathyroidectomy or patients with recurrent primary hyperparathyroidism after parathyroidectomy:

The usual starting dosage for adults is 2 mg of evocalcet administered orally once daily. The starting dose may be 2 mg twice daily, depending on the serum calcium level of the patient. The subsequent oral dose is adjusted, depending on the serum calcium level of the patient, and may be increased to a maximum of 6 mg 4 times daily.

(Underline denotes additions.)

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.

2. Since only a limited number of patients participated in clinical studies of the product in Japan, the applicant is required to conduct a post-marketing drug use-results survey involving all patients treated with the product until data from a specified number of patients have been gathered in order to understand the characteristics of patients treated with the product, and to collect safety and efficacy data as early as possible, so that necessary measures are taken to ensure proper use of the product.

Attachment

Review Report (1)

October 15, 2019

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Orkedia Tablets 1 mg Orkedia Tablets 2 mg
Non-proprietary Name	Evocalcet
Applicant	Kyowa Hakko Kirin Co., Ltd.
Date of Application	April 24, 2019
Dosage Form/Strength	Film-coated tablets: Each tablet contains 1 or 2 mg of Evocalcet
Proposed Indications	○ Secondary hyperparathyroidism in patients on maintenance dialysis ○ Hypercalcaemia in patients with any of the following conditions: • Parathyroid carcinoma • Primary hyperparathyroidism unable to be treated by parathyroidectomy or recurrent primary hyperparathyroidism after parathyroidectomy (Underline denotes additions.)

Proposed Dosage and Administration

Secondary hyperparathyroidism in patients on maintenance dialysis:
The usual starting dosage for adults is 1 mg of evocalcet administered orally once daily. The starting dose may be 2 mg once daily, depending on the patient's condition. The subsequent oral dose is adjusted within the range from 1 to 8 mg once daily while parathyroid hormone (PTH) and serum calcium levels of the patient are closely monitored. The dose may be increased up to 12 mg once daily if the patient has an inadequate response.

Hypercalcaemia in patients with parathyroid carcinoma and hypercalcaemia in patients with primary hyperparathyroidism who are unable to undergo parathyroidectomy or patients with recurrent primary hyperparathyroidism after parathyroidectomy:
The usual starting dosage for adults is 2 mg of evocalcet administered orally once daily. The starting dose may be 2 mg twice daily depending on the patient's condition. The subsequent oral dose is usually adjusted within the range of 2 to 6 mg once to 4 times daily while the serum calcium levels of the patient are closely monitored.

The dose is adjusted depending on the patient's condition, and may be increased to a maximum of 6 mg 4 times daily.

(Underline denotes additions.)

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Primary hyperparathyroidism (PHPT) is characterized by excessive parathyroid hormone (PTH) secretion which leads to increased serum calcium (Ca) levels, resulting in various symptoms such as renal impairment, gastrointestinal symptoms, muscular weakness, bone pain, nerve-related symptoms, and cardiovascular events. Main causes of PHPT include parathyroid adenoma or hyperplasia and parathyroid carcinoma. The first-line treatment for PHPT is parathyroidectomy (PTx), but recurrent PHPT occurs in some patients after PTx. Currently in Japan, a calcium receptor (CaR) agonist cinacalcet hydrochloride (cinacalcet) is approved for the treatment of hypercalcaemia in patients with parathyroid carcinoma and hypercalcaemia in patients with PHPT who are unable to undergo PTx or patients with recurrent PHPT after PTx (hereinafter collectively referred to as intractable PHPT). However, adverse drug reactions related to upper gastrointestinal disorder such as nausea and vomiting occur in a certain percentage of patients treated with cinacalcet, precluding administration of the cinacalcet dose that will allow these patients to achieve adequate response.

Evocalcet is a CaR agonist similar to cinacalcet. In Japan, evocalcet was approved in March 2018 for the indication for the treatment of secondary hyperparathyroidism in patients on maintenance dialysis. With the expectation that evocalcet is less prone to cause upper gastrointestinal disorder, a problem with cinacalcet, the clinical development of evocalcet as a therapeutic agent for the treatment of hypercalcaemia in parathyroid carcinoma and in intractable PHPT was undertaken.

Recently, the applicant submitted a partial change application based on the results of a Japanese clinical study, with the claim that the efficacy and safety of evocalcet have now been demonstrated.

Evocalcet is not approved in any foreign country as of September 2019.

Evocalcet was designated as an orphan drug on March 4, 2019 with the intended indication of "hypercalcaemia in patients with parathyroid carcinoma and hypercalcaemia in patients with primary hyperparathyroidism who are unable to undergo parathyroidectomy or patients with recurrent primary hyperparathyroidism after parathyroidectomy" (Orphan Drug Designation No. 426 of 2019 [*31 yaku*]).

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

Since the present application is for new indications and new dosages, "data relating to quality" were not submitted.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Although the present application is for new indications and new dosages, "non-clinical pharmacology data" were reviewed at the initial approval (Review Report of Orkedia Tablets 1 mg, etc. [February 19, 2018]), and, therefore, no new study data were submitted.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Although the present application is for new indications and new dosages, "non-clinical pharmacokinetic data" were reviewed at the initial approval (Review Report of Orkedia Tablets 1 mg, etc. [February 19, 2018]), and, therefore, no new study data were submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

Since the present application is for new indications and new dosages, "data of nonclinical toxicity studies" were not submitted.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

Although the formulation used in the clinical study whose data were submitted as the evaluation data for the present application is different from the approved film-coated formulation in components and contents, the bioequivalence of pre-change and post-change formulations has been demonstrated by a dissolution test (evaluated at the initial approval).

The concentration of unchanged evocalcet in plasma was measured by liquid chromatography-tandem mass spectrometry (LC/MS/MS). The lower limit of quantitation was 0.05 ng/mL.

6.2 Clinical pharmacology

6.2.1 Japanese phase III study (5.3.5.2-1, Study 7580-101 [October 2017 to April 2019])

The concentration of unchanged evocalcet in plasma following the oral administration was investigated in a Japanese study in patients with parathyroid carcinoma or intractable PHPT.

The starting dosage was 2 mg of evocalcet administered orally once or twice[1)] daily, followed by the daily dose of 2 to 24 mg, depending on the corrected serum Ca level.[2)] If corrected serum Ca levels were maintained at ≤10.3 mg/dL for 2 weeks within 24 weeks of treatment, the patient was allowed to switch from the evaluation period to the extension period and received evocalcet up to Week 52.

As for pharmacokinetics, Table 1 shows the C_{max} and t_{max} of unchanged evocalcet in plasma following the initial dose of evocalcet. Table 2 shows the C_{max} and t_{max} of unchanged evocalcet in plasma following multiple administration of evocalcet.

Table 1. Pharmacokinetic parameters of unchanged evocalcet in plasma following the initial oral dose of evocalcet 2 mg

	N	C_{max} (ng/mL)	t_{max}[a)] (h)
All patients	18	194 ± 66	1.0 (0.5, 3.0)
PTx-inoperable PHPT	13	200 ± 63	1.0 (0.5, 3.0)
Recurrent PHPT after PTx	2	205, 245 [b)]	1.0, 1.0[b)]
Parathyroid carcinoma	3	149 ± 91	2.1 (0.9, 2.9)

Mean ± standard deviation (SD)
a) Median (min, max)
b) Values observed in 2 patients

1) The starting dosage was selected according to the corrected serum Ca level at the screening test.
- ≤12.5 mg/L: 2 mg once daily (2 mg/day)
- >12.5 mg/L: 2 mg twice daily (4 mg/day)

2) If serum albumin level was <4.0 g/dL
Corrected serum Ca level (mg/dL) = serum Ca level (mg/dL) – serum albumin level (g/dL) + 4.0
If serum albumin level was ≥4.0 g/dL
Corrected serum Ca level (mg/dL) = serum Ca level (mg/dL)

Table 2. Pharmacokinetic parameters of unchanged evocalcet in plasma following the multiple oral administration of evocalcet

Dose	N	C_{max} (ng/mL)	t_{max}[a)] (h)
2 mg twice daily	4	184 ± 29	1.9 (1.0, 2.0)
4 mg twice daily	4	479 ± 43	1.0 (0.5, 1.0)
6 mg twice daily	4	1,100 ± 644	1.4 (1.0, 2.8)
6 mg 4 times daily	4	1,080 ± 658	0.8 (0.5, 2.9)

Mean ± SD
a) Median (min, max)

6.R Outline of the review conducted by PMDA

The applicant's explanation about the pharmacokinetics of evocalcet:

There appears to be no significant difference in the concentration of unchanged evocalcet in plasma following the initial dose of evocalcet among patients with different primary disease although data were obtained from an extremely small number of patients. In addition, although the concentration of unchanged evocalcet in plasma following the multiple administration of evocalcet varied substantially due to the small number of patients in each dose group, C_{max} generally tended to increase in proportion to dose.

These results suggest that plasma evocalcet concentration is unlikely to increase to such an extent as to affect safety following the multiple oral administration of 24 mg of evocalcet (6 mg 4 times daily).

PMDA accepted the explanation of the applicant.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted the data of the Japanese study (Study 7580-101) shown in Table 3 as the evaluation data.

Table 3. Outline of the efficacy and safety evaluation data

Study number	Study design	Patients	Treatment duration	Dose group (No. of patients treated)	Primary endpoint
7580-101	Open label, uncontrolled	Patients with parathyroid carcinoma or patients with PTx-inoperable PHPT or recurrent PHPT after PTx	52 weeks	Evocalcet (n = 18)	The number and the percentage of patients who maintained corrected serum Ca levels at ≤10.3 mg/dL for 2 weeks during the evaluation period: 14, 77.8%

7.1 Japanese phase III study (5.3.5.2-1, Study 7580-101 [October 2017 to April 2019])

A multicenter, open-label, uncontrolled study in patients with parathyroid carcinoma or intractable PHPT (Table 4) (target sample size, ≥10 subjects) was conducted at 14 study sites in Japan to investigate the efficacy and safety of evocalcet.

Table 4. Main inclusion/exclusion criteria

Main inclusion criteria: • Patients aged ≥20 years • Patients with parathyroid carcinoma or intractable PHPT • Corrected serum Ca levels >11.3 mg/dL at the screening test
Main exclusion criteria: • Patients who used cinacalcet within 2 weeks before the screening test • Patients who changed the dosage or the type of active vitamin D or its derivative or Ca formulation, or patients who newly received these drugs, within 2 weeks before the screening test • Patients with hypercalcaemia associated with malignancies other than parathyroid carcinoma

The study consisted of a screening period, an evaluation period of a maximum of 24 weeks after the start of evocalcet treatment, and the subsequent extension period up to Week 52. Patients who had maintained corrected serum Ca levels ≤10.3 mg/dL for 2 weeks before Week 24 were allowed to enter the extension period. Among the remaining patients, those considered eligible for the extended treatment by the investigator at Week 24 also entered the extension period. The duration of treatment with study drug, which consisted of the evaluation period and the extension period, was 52 weeks in total. Patients excluded from the entry in the extension period at the discretion of the investigator were withdrawn from the study at the end of the evaluation period at Week 24.

The treatment was started with 2 mg of evocalcet administered orally once or twice daily, and the subsequent oral doses were adjusted according to Table 5.

Table 5. Table for dose adjustment

<table>
<tr><td>Starting dosage</td><td>Selected according to corrected serum Ca levels at the screening test
• ≤12.5 mg/dL: 2 mg once daily (2 mg/day)
• >12.5 mg/dL: 2 mg twice daily (4 mg/day)</td></tr>
<tr><td>Range of dose adjustment</td><td><table><tr><th>Level</th><th>Dosage</th></tr><tr><td>1</td><td>2 mg once daily (2 mg/day)</td></tr><tr><td>2</td><td>2 mg twice daily (4 mg/day)</td></tr><tr><td>3</td><td>4 mg twice daily (8 mg/day)</td></tr><tr><td>4</td><td>6 mg twice daily (12 mg/day)</td></tr><tr><td>5</td><td>6 mg 3 times daily (18 mg/day)</td></tr><tr><td>6</td><td>6 mg 4 times daily (24 mg/day)</td></tr></table></td></tr>
<tr><td>Criteria for dose increase</td><td>Increase the dose by 1 level if all of the following criteria are met:
• Corrected serum Ca level at the visit is >10.3 mg/dL.
• The same dosage has continued for ≥2 weeks.
• The investigator judges that the dose increase will not pose any safety problem to the patient.</td></tr>
<tr><td>Criteria for dose reduction</td><td>• The investigator considers that the dose should be reduced because of an adverse event.
• Dose reduction by 1 level as a general rule. A reduction by >1 level is allowed if deemed appropriate by the investigator.
• The minimum dose is 2 mg once daily (2 mg/day).
• The treatment should be interrupted if dose reduction is deemed necessary in patients receiving 2 mg once daily (2 mg/day).</td></tr>
<tr><td>Dose increase after reduction</td><td>• The dose may be increased if deemed appropriate by the investigator.
• Dose increase by 1 level as a general rule. However, a dose increase by >1 level (but not more than the dosage used immediately before the dose reduction) is allowed if deemed necessary by the investigator.</td></tr>
<tr><td>Criteria for interruption</td><td>Treatment should be interrupted if any of the following criteria is met:
• Corrected serum Ca level has decreased to ≤7.5 mg/dL.
• The investigator considers that the treatment should be interrupted because of an adverse event.
• The investigator considers it necessary to reduce the dose for the patient on 2 mg once daily (2 mg/day).</td></tr>
<tr><td>Criteria for resuming administration after interruption</td><td>• Treatment may be resumed if corrected serum Ca level is ≥8.4 mg/dL and the investigator considers it possible to resume treatment by taking the safety of the patient into account.
• The treatment should be resumed at the same or lower level than that immediately before the interruption.
• The interruption period should not exceed consecutive 8 weeks.</td></tr>
</table>

All of the 18 patients (3 patients with parathyroid carcinoma and 15 patients with intractable PHPT) receiving evocalcet were included in the safety analysis population and the full analysis set (FAS), and the FAS was handled as the primary efficacy analysis population. Study discontinuation occurred in 3 patients (2 patients with parathyroid carcinoma and 1 patient with intractable PHPT). The reasons for the discontinuation were “adverse event,” “patient’s request,” and “the investigator’s judgement” in 1 patient each.

The number and the percentage [95% confidence interval (CI)] of patients who achieved the corrected serum Ca levels maintained at ≤10.3 mg/dL for 2 weeks during the evaluation period, the primary efficacy endpoint, was 14 of 18 patients and 77.8% [52.4%, 93.6%], showing that the lower limit of the 95% CI of the percentage of patients achieving the endpoint exceeded the pre-specified threshold (11%).

Adverse events were observed in all patients receiving evocalcet (18 patients). Table 6 shows adverse events reported in ≥2 patients. Adverse drug reactions were observed in 44.4% (8 of 18) of patients, as shown in Table 7.

Table 6. Adverse events reported in ≥2 patients

Adverse event	Evocalcet (N = 18)	Adverse event	Evocalcet (N = 18)
All adverse events	100 (18)	Influenza	11.1 (2)
Nasopharyngitis	38.9 (7)	Arthralgia	11.1 (2)
Nausea	16.7 (3)	Back pain	11.1 (2)
Chest pain	11.1 (2)	Myalgia	11.1 (2)
Cystitis	11.1 (2)	Headache	11.1 (2)

Medical dictionary for regulatory activities (MedDRA) ver. 21.1
Incidence, % (n)

Table 7. All adverse drug reactions observed

Adverse drug reaction	Evocalcet (N = 18)	Adverse drug reaction	Evocalcet (N = 18)
All adverse drug reactions	44.4 (8)	Viral infection	5.6 (1)
Nausea	11.1 (2)	Dysgeusia	5.6 (1)
Abdominal discomfort	5.6 (1)	Cough	5.6 (1)
Dyspepsia	5.6 (1)	Eczema	5.6 (1)
Vomiting	5.6 (1)	Hypertension	5.6 (1)

MedDRA ver. 21.1
Incidence, % (n)

No death occurred. Serious adverse events other than death were observed in 16.7% (3 of 18) of patients (enterocolitis, urinary tract infection, and uterine cancer in 1 patient each), and a causal relationship to evocalcet was ruled out for all of these events.

An adverse event leading to treatment discontinuation was observed in 1 patient (uterine cancer).

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

Based on the results of the reviews in Sections 7.R.1.1 through 7.R.1.4 shown below, PMDA considers that evocalcet is effective for the treatment of hypercalcaemia associated with parathyroid carcinoma or intractable PHPT.

7.R.1.1 Justification for conducting the Japanese study as an open-label, uncontrolled study

The applicant's explanation about the justification for planning and conducting the Japanese study as an open-label, uncontrolled study:

Parathyroid carcinoma occurs in ≤1 per 1 million people (*Ann Endocrinol [Paris]*. 2015;76:169-77, *Nat Rev Endocrinol.* 2012;8:612-22). The questionnaire survey was conducted by the Thyroid Surgery Study Group (currently the Japanese Society of Thyroid Surgery) from 1990 through 2000, and the results reported that there were 3,152 patients with PHPT. It is inferred that patients with intractable PHPT accounted for only a small proportion of them. In addition, given the seriousness of the disease, etc., it is practically impossible to choose the design of a controlled study. It is therefore justifiable that the Japanese study was conducted as an open-label, uncontrolled study.

PMDA's view:

Given the extremely small number of patients with parathyroid carcinoma or intractable PHPT and the seriousness of the diseases, it was unavoidable that the Japanese study was conducted as an open-label, uncontrolled study.

7.R.1.2 Primary endpoint in the Japanese study

The applicant's explanation about the justification for the primary endpoint of the Japanese study and about the results obtained:

There are no guidelines, etc., that define the target serum Ca level in the treatment of parathyroid carcinoma and intractable PHPT. The target for maintaining serum Ca levels below a certain level was determined by referring to the clinical study of cinacalcet. The primary endpoint was specified as the number and percentage of patients who maintained corrected serum Ca levels ≤10.3 mg/dL for 2 weeks during the evaluation period.

The lower limit of 95% CI of the primary endpoint was defined as >11% for the acceptance criteria for efficacy. This was based on the Japanese Phase III study of cinacalcet in patients with parathyroid carcinoma and intractable PHPT (Study KRN1493-101) and on the foreign placebo-controlled study of cinacalcet in patients with PTx-inoperable PHPT (*Eur J Endocrinol.* 2015;172:527-35).[3)]

In the Japanese study, the percentage [95% CI] of patients maintaining corrected serum Ca levels ≤10.3 mg/dL for 2 weeks during the evaluation period, the primary endpoint, was 77.8% [52.4%, 93.6%], showing that the lower limit of the 95% CI of the percentage of patients achieving the primary endpoint exceeded the pre-specified threshold (11%). Furthermore, the percentage of patients achieving the primary endpoint was similar to the value pre-estimated at the planning of the study (70%). The applicant considers that these findings have demonstrated the efficacy of evocalcet in the treatment of hypercalcaemia associated with parathyroid carcinoma or intractable PHPT.

PMDA's view:

There are no particular problems with the applicant's explanation about the primary endpoint of the Japanese study. The percentage [95% CI] of the patients maintaining corrected serum Ca levels ≤10.3 mg/dL for 2 weeks during the evaluation period, the primary endpoint, was 77.8% [52.4%, 93.6%], showing that the lower limit of the 95% CI of the percentage of patients achieving the primary endpoint exceeded the pre-specified threshold. These results, together with those classified by the primary disease [see Section 7.R.1.4], suggest that evocalcet is effective for the treatment of hypercalcaemia associated with parathyroid carcinoma or intractable PHPT.

7.R.1.3 Main secondary endpoints of the Japanese study

PMDA confirmed that the results of the secondary endpoints of the Japanese study were generally consistent with the results of the primary endpoint, based on the results of reviews in Sections 7.R.1.3.1 and 7.R.1.3.2. PMDA also confirmed that the efficacy of evocalcet in normalizing corrected serum Ca levels tends to be maintained during the extension period.

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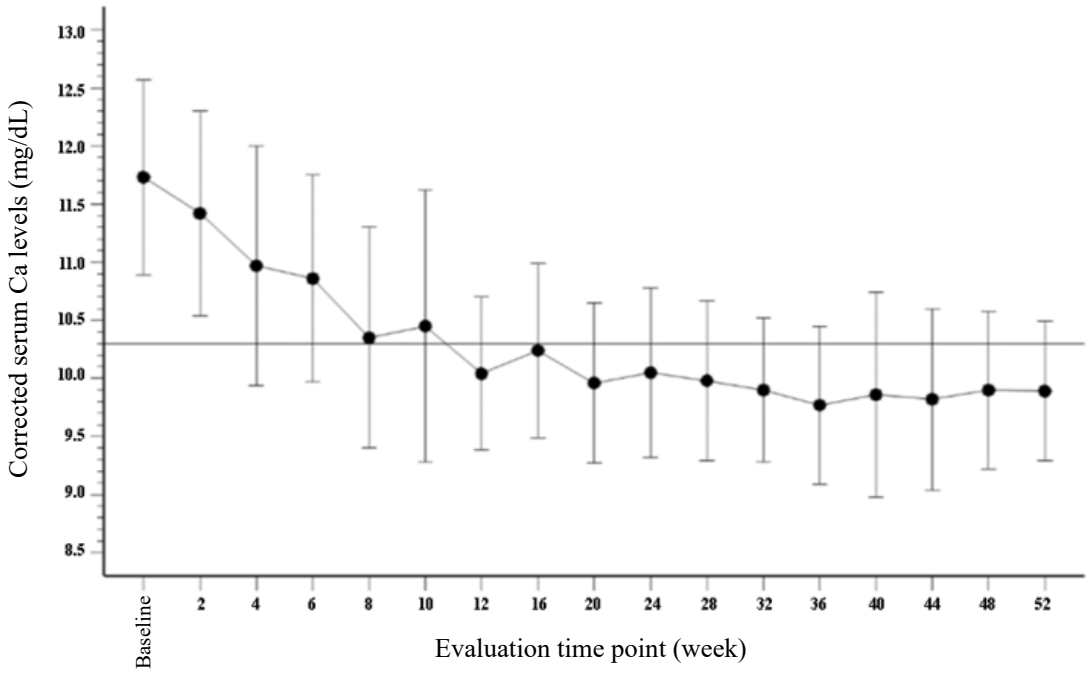
3) In the placebo group, none of the 34 patients (0%) achieved corrected serum calcium levels ≤10.3 mg/dL during the evaluation period. Based on this result, the applicant calculated the upper limit of 95% CI of the percentage of patients achieving the primary endpoint in the placebo group to be 10.3%.

7.R.1.3.1 Serum Ca levels

"The number and percentage [95% CI] of patients who had a decrease of ≥1.0 mg/dL from baseline in corrected serum Ca levels and maintained the decreased level for 2 weeks during the evaluation period," a secondary endpoint of the Japanese study, were 12 of 18 patients and 66.7% [41.0%, 86.7%], respectively. Figure 1 shows the time course of the mean corrected serum Ca level up to Week 52, and Table 8 shows changes from baseline.



Evaluation time point (week)	Baseline	2	4	6	8	10	12	16	20	24	28	32	36	40	44	48	52
Number of patients	18	18	18	18	18	14	17	17	15	15	15	15	15	15	15	15	15

Figure 1. Time course of corrected serum Ca levels (mean ± SD) (Japanese study, FAS)

Table 8. Change in corrected serum Ca levels from baseline (Japanese study, FAS)

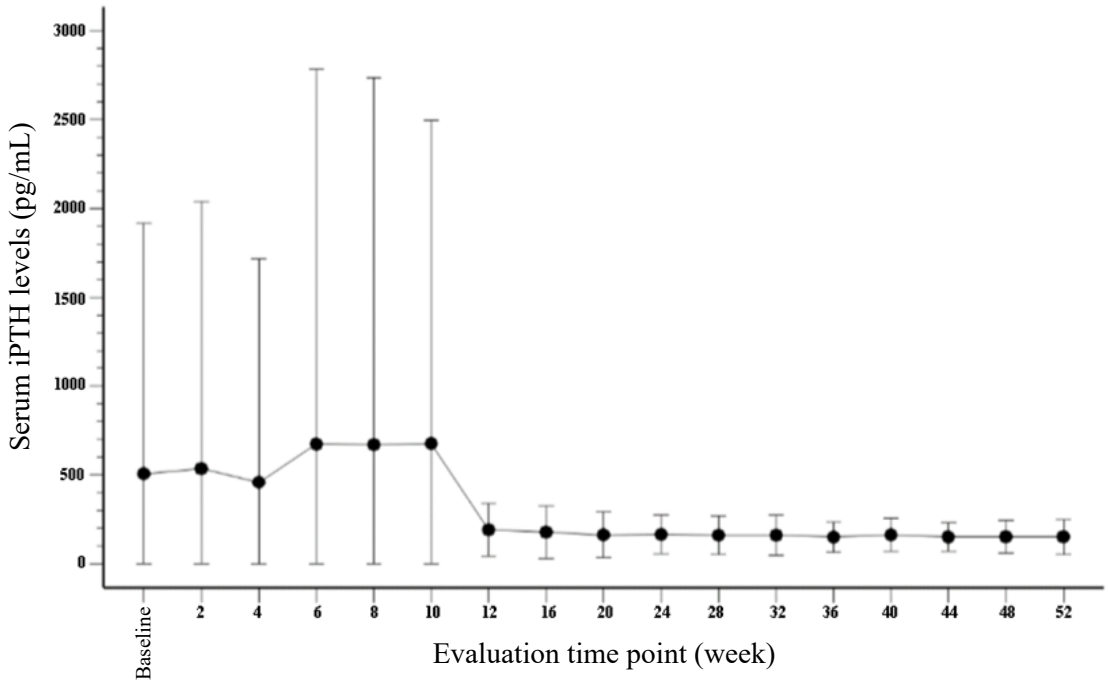
Evaluation time point	N	Corrected serum Ca levels (mg/dL)	Change from baseline (mg/dL)
Baseline	18	11.73 ± 0.84	-
Week 24	15	10.05 ± 0.73	-1.55 ± 0.92
Week 52	15	9.89 ± 0.60	-1.71 ± 0.52

Mean ± SD

Based on the above results, PMDA confirmed that, in the Japanese study, the mean corrected serum Ca level decreased over time after the start of treatment with evocalcet and remained at ≤10.3 mg/dL from Week 24 onward.

7.R.1.3.2 iPTH levels

Figure 2 shows the time course of the mean serum intact parathyroid hormone (iPTH) level up to Week 52 in the Japanese study. One patient[4)] who showed a much higher serum iPTH level than other patients discontinued the study at Week 10. As a result, the mean serum iPTH level dropped at Week 12 and remained at a similar level thereafter.



Evaluation time point (week)	Baseline	2	4	6	8	10	12	16	20	24	28	32	36	40	44	48	52
Number of patients	18	18	18	18	18	14	17	17	15	15	15	15	15	15	15	15	15

Figure 2. Time course of serum iPTH levels (mean ± SD) (Japanese study, FAS)

PMDA asked the applicant to explain the reason why there was no clear tendency toward a decrease in serum iPTH levels in response to treatment with evocalcet.

The applicant's explanation:
In the Japanese phase I studies in healthy adults (Studies 7580-001 and 7580-002), a maximum decrease in serum iPTH levels was shown within 4 hours after administration of evocalcet, but this effect of evocalcet was short-lasting. In the Japanese study, blood samples were collected immediately before administration of evocalcet. This may have resulted in no clear decrease in serum iPTH levels following administration of evocalcet.

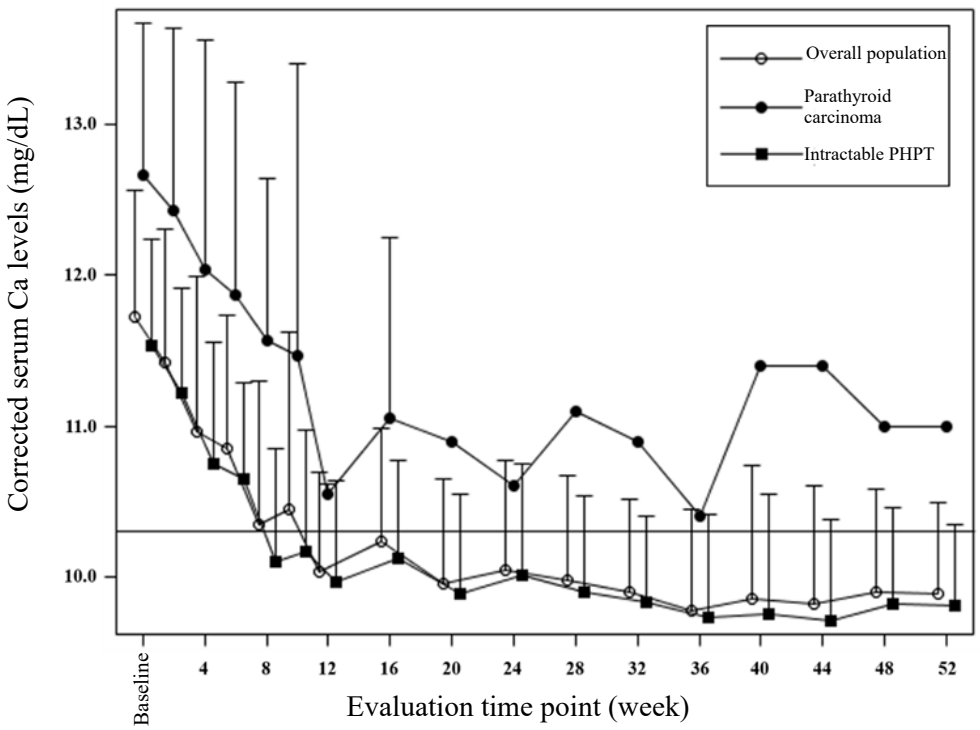
PMDA accepted the explanation of the applicant.

[4)] A 32-year-old male patient. Baseline serum iPTH level was 6,140 pg/mL. During the treatment with evocalcet, serum iPTH levels remained within the range from 5,480 to 9,110 pg/mL. The study was discontinued on Day 76 at the discretion of the investigator due to the exacerbation of parathyroid carcinoma.

7.R.1.4 Efficacy by primary disease

The applicant's explanation about the efficacy of evocalcet by the primary disease:

Figure 3 shows the time course of corrected serum Ca levels up to Week 52, classified by the primary disease. Table 9 shows the efficacy during the evaluation period, classified by the primary disease.



Evaluation time point (week)		Baseline	2	4	6	8	10	12	16	20	24	28	32	36	40	44	48	52
Number of patients	Overall	18	18	18	18	18	14	17	17	15	15	15	15	15	15	15	15	15
	Parathyroid carcinoma	3	3	3	3	3	3	2	2	1	1	1	1	1	1	1	1	1
	Intractable PHPT	15	15	15	15	15	11	15	15	14	14	14	14	14	14	14	14	14

Figure 3. Time course of corrected serum Ca levels (mean ± SD) (Japanese study, FAS)

Table 9. Efficacy during the evaluation period, classified by the primary disease

Primary disease	Primary endpoint	Secondary endpoint
	Percentage of patients who maintained corrected serum Ca levels ≤10.3 mg/dL for 2 weeks	Percentage of patients who showed a decrease of ≥1.0 mg/dL from baseline in corrected serum Ca levels and maintained the decreased level for 2 weeks
Total (N = 18)	77.8 [52.4, 93.6] (14/18)	66.7 [41.0, 86.7] (12/18)
Parathyroid carcinoma (N = 3)	0 [0, 70.8] (0/3)	66.7 [9.4, 99.2] (2/3)
Intractable PHPT (N = 15)	93.3 [68.1, 99.8] (14/15)	66.7 [38.4, 88.2] (10/15)

Percentage of patients [95% CI]: % (n/N)

The applicant confirmed that evocalcet is expected to be effective in patients with intractable PHPT. In patients with parathyroid carcinoma, the number and the percentage of patients who maintained corrected serum Ca levels ≤10.3 mg/dL for 2 weeks during the evaluation period, the primary endpoint, was 0 of 3 patients and 0%, respectively. However, taking account of the observation that (1) there were only an extremely small number of patients investigated, (2) the baseline Ca level was higher in

patients with parathyroid carcinoma than in patients with intractable PHPT, and (3) corrected serum Ca levels decreased from baseline and the decreased level was maintained throughout the evaluation period, evocalcet is expected to be effective in patients with parathyroid carcinoma as well.

PMDA's view:
In patients with intractable PHPT, evocalcet is expected to be effective without any tendency of clinically significant problems.

None of patients with parathyroid carcinoma achieved the primary endpoint, and this is considered to be partly due to the fact that the baseline corrected serum Ca level was evidently higher in those patients than in patients with intractable PHPT (12.67 ± 1.01 mg/dL [mean ± standard deviation (SD)] in patients with parathyroid carcinoma, 11.54 ± 0.7 mg/dL in patients with intractable PHPT). A decrease of ≥1.0 mg/dL from baseline in the mean corrected serum Ca level at Week 8 was observed both in patients with parathyroid carcinoma and in patients with intractable PHPT, and the change from baseline in corrected serum Ca levels at Week 8 was similar between the two patient populations (−1.10 ± 0.52 mg/dL [mean ± SD] in patients with parathyroid carcinoma, −1.43 ± 0.81 mg/dL in patients with intractable PHPT). Although there are limitations to the interpretation of the results because of the extremely small number of patients studied, the results suggest that evocalcet is effective in patients with parathyroid carcinoma as well.

7.R.2 Safety

Based on the reviews in Sections 7.R2.1 through 7.R.2.3 below, PMDA considers that the safety of evocalcet in patients with parathyroid carcinoma and patients with intractable PHPT is acceptable. However, in consideration of the extremely small number of patients enrolled in the Japanese study, information on events related to upper gastrointestinal disorder and events related to hypercalcaemia should be collected continuously in the post-marketing surveillance, etc.

7.R.2.1 Incidence of adverse events in the Japanese study

Table 6 shows adverse events reported in ≥2 patients in the Japanese study. All of the events were mild to moderate in severity. Table 7 shows adverse drug reactions observed. All of them were mild. Serious adverse events were observed in 16.7% (3 of 18) of patients (enterocolitis, urinary tract infection, and uterine cancer in 1 patient each), but these adverse events were considered unrelated to evocalcet.

Table 10 shows the incidence of adverse events classified by treatment period in the Japanese study. There was no tendency toward an increase in adverse events with prolonged duration of treatment with evocalcet. Based on the above findings, PMDA considers that there is no clinically significant problem in the safety of evocalcet.

Table 10. Incidence of adverse events by treatment period

		Week 1-13	Week 14-26	Week 27-39	Week 40-52	Entire period
		N = 18	N = 17	N = 15	N = 15	N = 18
Adverse events		83.3 (15)	58.8 (10)	66.7 (10)	46.7 (7)	100 (18)
Adverse drug reactions		38.9 (7)	5.9 (1)	6.7 (1)	6.7 (1)	44.4 (8)
Death		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Serious adverse events other than death		5.6 (1)	11.8 (2)	0 (0)	0 (0)	16.7 (3)
Serious adverse drug reactions other than death		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Adverse events leading to treatment discontinuation		0 (0)	5.9 (1)	0 (0)	0 (0)	5.9 (1)
Adverse drug reactions leading to treatment discontinuation		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Events related to upper gastrointestinal disorder[a)]		27.8 (5)	0 (0)	0 (0)	0 (0)	27.8 (5)
	Nausea	16.7 (3)	0 (0)	0 (0)	0 (0)	16.7 (3)
	Abdominal discomfort	5.6 (1)	0 (0)	0 (0)	0 (0)	5.6 (1)
	Vomiting	5.6 (1)	0 (0)	0 (0)	0 (0)	5.6 (1)
	Abdominal distension	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Decreased appetite	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Abdominal pain upper	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Events related to hypocalcaemia[b)]		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

MedDRA ver. 21.1
Incidence, % (n)
a) Preferred terms of MedDRA; "nausea," "abdominal discomfort" "vomiting," "abdominal distension," "decreased appetite," and "abdominal pain upper"
b) Preferred terms of MedDRA; "blood calcium decreased," "corrected calcium decreased," and "hypocalcaemia"

7.R.2.2 Comparison with data from the clinical studies involving patients with secondary hyperparathyroidism

The proposed dosage for hypercalcaemia associated with parathyroid carcinoma or intractable PHPT exceeds the dosage approved for secondary hyperparathyroidism (SHPT) in patients on maintenance dialysis. Therefore, PMDA asked the applicant to explain the necessity of further precautions in addition to those for the treatment of SHPT in patients on maintenance dialysis, by comparing the safety profile of evocalcet in patients with parathyroid carcinoma or intractable PHPT with that in patients with SHPT on maintenance dialysis.

The applicant's explanation:

Table 11 shows the incidence of adverse events observed in the Japanese study in patients with parathyroid carcinoma or intractable PHPT and those observed in the Japanese clinical study in patients with SHPT on maintenance dialysis. The incidence of overall adverse events was similar between the two studies, whereas nasopharyngitis (*jointoen*) was reported only in patients with parathyroid carcinoma or intractable PHPT (38.9% [7 of 18] of patients), and nasopharyngitis (*biintoen*) only in patients with SHPT on maintenance dialysis (41.0% [202 of 493] of patients). These adverse events are considered to be generally similar to each other. The observed difference in the incidences of these adverse events is attributed to the different Japanese terms used for the same symptom (nasopharyngitis) in the different versions of medical dictionary for regulatory activities (MedDRA) in Japanese (MedDRA ver. 21.1 versus MedDRA ver. 19.0). There was no significant difference in the incidence of pharyngitis between the two populations. Furthermore, the incidence of overall adverse drug reactions was similar between the two populations, with no adverse drug reaction showing clearly higher incidence in one population than in the other.

The above results suggest that no additional precautions are required in patients with parathyroid carcinoma or intractable PHPT.

Table 11. Adverse events reported in ≥3% of patients with either of the diseases

	Parathyroid carcinoma or intractable PHPT	SHPT on maintenance dialysis
	Japanese study (N = 18)	Pooled analysis[a)] (N = 493)
Overall adverse events	100 (18)	93.9 (463)
Overall adverse drug reactions	44.4 (8)	42.2 (208)
Death	0 (0)	0.4 (2)
Serious adverse events other than death	16.7 (3)	23.1 (114)
Serious adverse drug reactions other than death	0 (0)	2.4 (12)
Adverse events leading to treatment discontinuation	5.9 (1)	7.1 (35)
Adverse drug reactions leading to treatment discontinuation	0 (0)	1.8 (9)
Adverse events		
Nasopharyngitis (*jointoen*)	38.9 (7)	0 (0)
Nausea	16.7 (3)	8.1 (40)
Arthralgia	11.1 (2)	6.1 (30)
Influenza	11.1 (2)	4.3 (21)
Back pain	11.1 (2)	3.9 (19)
Headache	11.1 (2)	3.2 (16)
Myalgia	11.1 (2)	2.6 (13)
Chest pain	11.1 (2)	1.2 (6)
Cystitis	11.1 (2)	1.0 (5)
Vomiting	5.6 (1)	8.5 (42)
Abdominal discomfort	5.6 (1)	5.5 (27)
Pain in extremity	5.6 (1)	4.1 (20)
Pruritus	5.6 (1)	3.7 (18)
Gastroenteritis	5.6 (1)	3.2 (16)
Hypertension	5.6 (1)	3.0 (15)
Bronchitis	5.6 (1)	2.8 (14)
Dental caries	5.6 (1)	2.8 (14)
Stomatitis	5.6 (1)	2.8 (14)
Cough	5.6 (1)	2.6 (13)
Eczema	5.6 (1)	2.6 (13)
Iron deficiency anaemia	5.6 (1)	2.0 (10)
Faeces soft	5.6 (1)	1.8 (9)
Conjunctivitis	5.6 (1)	1.8 (9)
Pneumonia	5.6 (1)	1.6 (8)
Cataract	5.6 (1)	1.4 (7)
Dyspepsia	5.6 (1)	1.2 (6)
Hordeolum	5.6 (1)	1.2 (6)
Spinal compression fracture	5.6 (1)	1.0 (5)
Enterocolitis	5.6 (1)	0.8 (4)
Urticaria	5.6 (1)	0.8 (4)
Ocular hyperaemia	5.6 (1)	0.6 (3)
Tooth fracture	5.6 (1)	0.6 (3)
Atrial fibrillation	5.6 (1)	0.4 (2)
Abdominal pain lower	5.6 (1)	0.4 (2)
Urinary tract infection	5.6 (1)	0.4 (2)
Upper respiratory tract infection	5.6 (1)	0.2 (1)
Blood creatinine increased	5.6 (1)	0.2 (1)
Dysgeusia	5.6 (1)	0.2 (1)
Nasopharyngitis (*biintoen*)	0 (0)	41.0 (202)
Contusion	0 (0)	11.4 (56)
Corrected calcium decreased	0 (0)	11.0 (54)
Diarrhoea	0 (0)	9.3 (46)
Upper respiratory tract inflammation	0 (0)	6.3 (31)
Shunt stenosis	0 (0)	5.7 (28)
Wound	0 (0)	4.5 (22)

		Parathyroid carcinoma or intractable PHPT	SHPT on maintenance dialysis
		Japanese study (N = 18)	Pooled analysis[a)] (N = 493)
	Excoriation	0 (0)	4.3 (21)
	Shunt occlusion	0 (0)	3.9 (19)
	Blood calcium decreased	0 (0)	3.7 (18)
	Pharyngitis	0 (0)	3.7 (18)
	Muscle spasms	0 (0)	3.4 (17)
	Skin exfoliation	0 (0)	3.2 (16)

PHPT, MedDRA ver. 21.1; SHPT, MedDRA ver. 19.0
Incidence, % (n)
a) Japanese phase III comparative study of evocalcet involving SHPT patients on HD (Study 7580-010), Japanese long-term treatment study of evocalcet in SHPT patients on HD (Study 7580-011), and Japanese open-label clinical study in patients on PD (Study 7580-012)

PMDA's view:
Because of the extremely small number of patients with parathyroid carcinoma or intractable PHPT enrolled in the Japanese study, there are limitations to the comparison between the patient population proposed for the present application and patients with SHPT on maintenance dialysis, the disease for which evocalcet is approved. Nevertheless, there are currently no new events of concerns in patients with parathyroid carcinoma or intractable PHPT.

7.R.2.3 Adverse events of special interest

Based on the mechanism of action of evocalcet and on the results of nonclinical and clinical studies, PMDA evaluated adverse events related to upper gastrointestinal disorder and events related to hypocalcemia as adverse events of special interest, as described in Sections 7.R.2.3.1 and 7.R.2.3.2.

7.R.2.3.1 Adverse events related to upper gastrointestinal disorder

PMDA asked the applicant to explain the incidence of adverse events related to upper gastrointestinal disorder in the Japanese study.

The applicant's explanation:
Table 12 shows the incidences of adverse events related to upper gastrointestinal disorder (preferred terms of MedDRA, "abdominal discomfort," "abdominal distension," "nausea," "vomiting," "decreased appetite," and "abdominal pain upper"). Adverse events related to upper gastrointestinal disorder were observed in 27.8% (5 of 18) of the overall patient population, but all of the events were mild in severity.

Table 12. Events related to upper gastrointestinal disorder (Japanese study, safety analysis population)

Adverse event	Evocalcet (N = 18)
Events related to upper gastrointestinal disorder	27.8 (5)
Nausea	16.7 (3)
Abdominal discomfort	5.6 (1)
Vomiting	5.6 (1)
Abdominal distension	0 (0)
Decreased appetite	0 (0)
Abdominal pain upper	0 (0)

MedDRA ver. 21.1
Incidence, % (n)

PMDA considers that there is no clinically significant problem because all of the events related to upper gastrointestinal disorder observed in the Japanese study were mild. In view of the extremely

small number of patients enrolled in the Japanese study, relevant information should be collected continuously in the post-marketing surveillance, etc.

7.R.2.3.2 Events related to hypocalcaemia

Events related to hypocalcaemia may occur if serum Ca levels are decreased excessively by evocalcet. Therefore, the current package insert provides precautions against occurrence of events related to hypocalcaemia. In the Japanese phase III studies on evocalcet in patients with SHPT (Studies 7580-010, 7580-011, and 7580-012), hypocalcaemia-related events for which a causal relationship to evocalcet could not be ruled out were observed in 16.8% (83 of 493) of patients. PMDA asked the applicant to explain the incidences of hypocalcaemia-related events in the Japanese study in patients with parathyroid carcinoma or intractable PHPT.

The applicant's explanation:
In the Japanese study, events related to hypocalcaemia (preferred terms of MedDRA; "blood calcium decreased," "corrected calcium decreased," and "hypocalcaemia") were not observed. Arhythmia associated with QT/QTc prolongation that may be attributable to a decrease in blood Ca levels, adverse events suggestive of pro-arrhythmic potential, and lenticular opacities was also investigated. The results showed that neither arrhythmia associated with QT/QTc prolongation nor adverse events suggestive of pro-arrhythmic potential were observed in the Japanese study. Cataract and cataract cortical were reported in 1 patient each as adverse events related to lenticular opacities. They were moderate and mild, respectively, in severity, and the events were considered unrelated to evocalcet.

Serum Ca levels should be measured periodically in patients with PHPT receiving evocalcet, as advised in the current package insert.

PMDA's view:
PMDA confirmed that neither hypocalcaemia nor adverse events associated with hypocalcaemia show any particularly problematic tendency. However, since evocalcet may cause an excessive decrease in serum Ca levels, serum Ca levels should be checked periodically in patients with parathyroid carcinoma or intractable PHPT as advised in the current package insert. Patients should be monitored for the risk of hypocalcaemia and associated adverse events. Because of the extremely small number of patients investigated in the Japanese study, information on the incidence of hypocalcaemia and associated adverse events should be collected continuously in the post-marketing surveillance, etc.

7.R.3 Clinical positioning

The applicant's explanation about the clinical positioning of evocalcet:
In Japan, cinacalcet is used for the treatment of hypercalcaemia in patients with parathyroid carcinoma or intractable PHPT. However, upper gastrointestinal disorders such as nausea and vomiting occur in a certain percentage of PHPT patients treated with cinacalcet, precluding administration of the cinacalcet dose that will allow these patients to achieve adequate response.

In the Japanese study of evocalcet in patients with parathyroid carcinoma or intractable PHPT, events related to upper gastrointestinal disorder were observed in 27.8% (5 of 18) of patients. In contrast, in

the Japanese phase III study (Study KRN1493-101) and the foreign phase II study of cinacalcet (Study AMG 073 20000204) in patients with parathyroid carcinoma or intractable PHPT, events related to upper gastrointestinal disorder were observed in 85.7% (6 of 7) of patients and 80.4% (37 of 46) of patients, respectively (Review Report of Regpara Tablets 25 mg, etc. [dated December 5, 2013]).

In the Japanese phase III study of evocalcet in patients with SHPT on HD (Study 7580-010), an indication different from that addressed in the present application, the incidence of upper gastrointestinal disorder was lower in the evocalcet group than in the cinacalcet group (18.6% [59 of 317] of patients in the evocalcet group, 32.8% [104 of 317] of patients in the cinacalcet group) (Review Report of Orkedia Tablets 1 mg, etc. [dated February 19, 2018]).

Since cinacalcet is metabolized mainly by CYP3A4 and strongly inhibits CYP2D6, the package insert of cinacalcet cautions against co-administration with CYP3A4 inhibitors (such as azole antifungal agents) or with CYP2D6 substrate drugs (such as tricyclic antidepressants). In contrast, evocalcet can be concomitantly administered with CYP3A4 inhibitors and with CYP2D6 substrate drugs because both the contribution of CYP isoforms to evocalcet metabolism and the inhibitory activity of evocalcet against CYP isoforms are extremely low.

On the above basis, evocalcet is expected to be useful as a drug for the treatment of hypercalcaemia associated parathyroid carcinoma or intractable PHPT with the same clinical positioning as cinacalcet, while the incidence of upper gastrointestinal disorder will be lower with evocalcet than with cinacalcet. In addition, evocalcet can be concomitantly administered with CYP3A4 inhibitors or CYP2D6 substrate drugs.

PMDA's view:
Results of the Japanese study suggested the efficacy of evocalcet in the treatment of hypercalcaemia associated with parathyroid carcinoma or intractable PHPT [see Section 7.R.1] and confirmed the safety of evocalcet in patients with parathyroid carcinoma or intractable PHPT [see Section 7.R.2]. These results demonstrate that evocalcet serves as a treatment option for hypercalcaemia in patients with parathyroid carcinoma or intractable PHPT.

In addition, PMDA confirmed that the incidence of upper gastrointestinal disorder is not clearly higher with evocalcet than with cinacalcet although there is no study of head-to-head comparison between evocalcet and cinacalcet in patients with parathyroid carcinoma or intractable PHPT.

7.R.4 Indications

The efficacy of evocalcet was shown in patients with parathyroid carcinoma or intractable PHPT in the Japanese study [Section 7.R.1] with an acceptable safety profile [Section 7.R.2]. PMDA therefore considers that the proposed indication of evocalcet (the treatment of hypercalcaemia in patients with parathyroid carcinoma and hypercalcaemia in patients with primary hyperparathyroidism who are unable to undergo parathyroidectomy or patients with recurrent primary hyperparathyroidism after parathyroidectomy) is acceptable.

7.R.5 Dosage and administration

Based on the reviews in Sections 7.R.5.1 through 7.R.5.3 presented below, PMDA considers that there is no particular problem in specifying the dosage and administration employed in the Japanese study and in adjusting the dose by an increment or decrement of 1 mg when serum Ca levels are not adequately controlled.

7.R.5.1 Starting dosage

The applicant's explanation about the justification for the starting dosage of evocalcet:

Because of the extremely small number of patients with parathyroid carcinoma or intractable PHPT [Section 7.R.1.1], it was considered infeasible to conduct a dose-finding study in patients with these diseases. Therefore, the dosage of evocalcet in the Japanese study (Study 7580-101) was determined based on the Japanese phase II study of evocalcet (Study 7580-005) in patients on hemodialysis and the Japanese phase III study of cinacalcet (Study KRN1493-101) in patients with parathyroid carcinoma or intractable PHPT.

Results of the Japanese phase II study of evocalcet (Study 7580-005) in patients on hemodialysis suggested that evocalcet 2 mg and cinacalcet 25 mg had a similar efficacy in decreasing iPTH and corrected serum Ca levels (Review Report of Orkedia Tablets 1 mg, etc. [February 19, 2018]). In the Japanese phase III study of cinacalcet (Study KRN1493-101), the inclusion criterion related to corrected serum Ca levels was >11.3 mg/dL for patients with parathyroid carcinoma and >12.5 mg/dL for patients with intractable PHPT. In the Japanese study (Study 7580-101), however, the inclusion criterion related to corrected serum Ca levels was >11.3 mg/dL for both patient groups to allow inclusion of patients with intractable PHPT with lower corrected serum Ca levels, taking account of the clinical practice at the time of planning the study.

Based on the above, the starting dosage in the Japanese study on evocalcet (Study 7580-101) was evocalcet 2 mg once daily, a lower dosage than 2 mg twice daily which is considered to correspond to the starting dosage employed in the Japanese phase III study of cinacalcet (Study KRN1493-101) (cinacalcet 25 mg twice daily). In patients with corrected serum Ca levels >12.5 mg/dL at the screening test, the starting dosage was evocalcet 2 mg twice daily because more prompt treatment of hypercalcaemia was deemed necessary.

In the Japanese study, the mean corrected serum Ca level decreased over time during treatment with evocalcet, reaching ≤10.3 mg/dL at Week 12. Adverse events observed within 14 days of administration in the Japanese study were classified by the starting dosage. Abdominal discomfort was observed in 1 of 16 patients in the subgroup starting with evocalcet 2 mg once daily, whereas no adverse event was observed in the subgroup (2 patients) starting with 2 mg twice daily. These results, albeit conducted in an extremely small number of patients, suggest that the difference in the starting dosage of evocalcet is unlikely to affect the incidence of adverse events.

As described above, in the Japanese study, the mean corrected serum Ca level tended to decrease after administration of evocalcet 2 mg once or twice daily as the starting dosage, and the safety of the

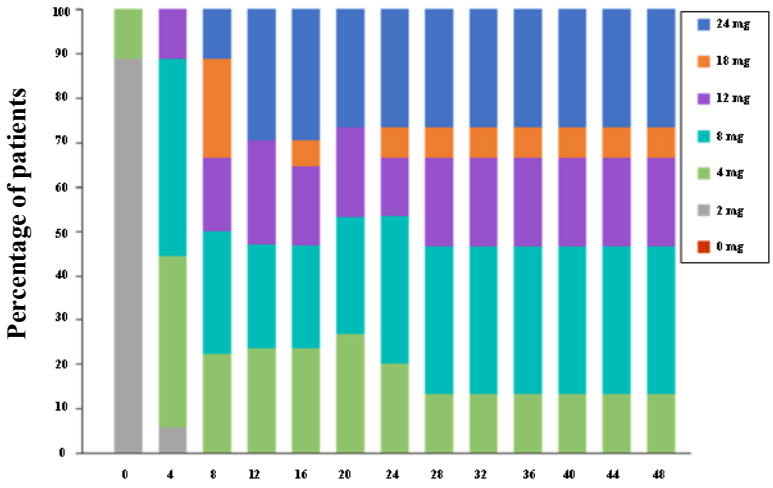
treatment was demonstrated. The applicant therefore considered that it is justifiable to specify the starting dosage of evocalcet 2 mg once or twice daily depending on serum Ca levels.

PMDA's view:
Judging from the results of the Japanese study and the explanation of the applicant, there is no particular problem in selecting the usual starting dosage of evocalcet 2 mg once daily and, depending on the patient's condition (if corrected serum Ca level is ≥12.5 mg/dL), in selecting the starting dosage of 2 mg twice daily.

7.R.5.2 Dose adjustment

The applicant's explanation about the procedures for dose adjustment of evocalcet:
The procedures for dose adjustment of evocalcet (Table 5) in the Japanese study (Study 7580-101) were specified by referring to the Japanese phase III study of cinacalcet (Study KRN1493-101) in patients with parathyroid carcinoma or intractable PHPT.

Figure 1 shows the time course of corrected serum Ca levels in the Japanese study. The mean corrected serum Ca level was maintained at ≤10.3 mg/dL from Week 12 up to Week 52 by adjusting the dose depending on corrected serum Ca levels, in accordance with the procedures for dose adjustment. Figure 4 shows the time course of the dose of evocalcet, which shows that the daily dose was distributed widely over the range from 2 mg (2 mg once daily) to 24 mg (6 mg 4 times daily).



Time after start of administration (weeks)

Time after start of administration (weeks)	0	4	8	12	16	20	24	28	32	36	40	44	48
Number of patients	18	18	18	17	17	15	15	15	15	15	15	15	15

Figure 4. Time course of the dose of evocalcet (Japanese study)

As for safety, the incidence of adverse events did not show any tendency toward an increase with prolonged duration of treatment [Section 7.R.2.1].

Based on the above, the applicant considered it appropriate to specify the criteria for dose adjustment of evocalcet (Table 5) in line with the Japanese study. In the Japanese study, the increment/decrement

of 2 mg per dose was used. However, if it is difficult to control serum Ca levels by this procedure,[5] physicians can opt to adjust the dose by an increment/decrement of 1 mg.

It will be appropriate to advise physicians to measure serum Ca levels, desirably at the start of treatment with evocalcet, once every 2 weeks before and after dose adjustment, and periodically during the maintenance period.

PMDA's view:
Since the Japanese study suggested the efficacy of evocalcet without any significant safety problem, there is no particular problem in adjusting the dose in line with the Japanese study and in adjusting the dose by an increment/decrement of 1 mg when serum Ca level is poorly controlled by the current dose.

7.R.5.3 Maximum dosage

The applicant's explanation about the justification for the maximum dosage of evocalcet:
It was considered necessary to specify the maximum dosage of evocalcet in the Japanese study (Study 7580-101) as 6 mg 4 times daily (corresponding to cinacalcet 75 mg 4 times daily), by taking account of the following: (1) In the Japanese phase III study of cinacalcet (Study KRN1493-101) in patients with parathyroid carcinoma or intractable PHPT, the maximum dose of cinacalcet was 75 mg 4 times daily, and (2) some of the patients with parathyroid carcinoma suffer from severe hypercalcaemia. Although there was no clinical experience of the dosage exceeding evocalcet 12 mg twice daily or once daily, the maximum dose in the Japanese study (Study 7580-101) was 24 mg (6 mg 4 times daily) with the assumption that the safety of patients would be ensured by the frequent and appropriate monitoring of serum Ca levels.

Figure 1 shows the time course of the dose of evocalcet in the Japanese study. Evocalcet was administered at the maximum dosage in 26.7% to 29.4% of patients during each treatment period from Week 12. Table 13 shows the incidence of adverse events by dose. There was no significant difference in the incidence of adverse drug reactions among groups receiving different dose at the onset of the adverse drug reactions.

These results suggest that it is appropriate to specify the maximum dosage of evocalcet at 6 mg 4 times daily.

[5] When either of the following conditions applies: (1) A dose increase is necessary because of an inadequate decrease in serum Ca levels by the current dose, but an increment of ≥2 mg may possibly cause an excessive decrease in serum Ca levels, or (2) a dose decrease is necessary because of an excessive decrease in serum Ca levels by the current dose, but a decrement of ≥2 mg may possibly result in an inadequate decrease in serum Ca levels.

Table 13. Incidences of adverse events by dose

	2 mg (N = 16)	4 mg (N = 18)	8 mg (N = 17)	12 mg (N = 11)	18 mg (N = 8)	24 mg (N = 6)
Adverse events	6.3 (1)	44.4 (8)	47.1 (8)	72.7 (8)	37.5 (3)	100 (6)
Adverse drug reactions	6.3 (1)	11.1 (2)	17.6 (3)	18.2 (2)	12.5 (1)	16.7 (1)
Serious adverse events other than death	0 (0)	0 (0)	0 (0)	18.2 (2)	0 (0)	16.7 (1)
Serious adverse drug reactions other than death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Adverse events leading to treatment discontinuation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	16.7 (1)
Adverse drug reactions leading to treatment discontinuation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Events related to upper gastrointestinal disorder[a)]	6.3 (1)	11.1 (2)	5.9 (1)	9.1 (1)	0 (0)	0 (0)

Incidence, % (n)

a) Preferred terms of MedDRA; "nausea," "abdominal discomfort," "abdominal distension," "vomiting," "decreased appetite," and "abdominal pain upper"

PMDA's view:

A certain number of patients ended up receiving evocalcet 6 mg 4 times daily as a result of a stepwise dose increase according to the dose adjustment criteria employed in the Japanese study (Table 5). No particular safety problem was noted. In view of these results and of the procedures for dose adjustment of evocalcet where the dose is increased, as appropriate, in a stepwise manner after checking serum Ca levels and other conditions, PMDA considers it appropriate to specify the maximum dosage of evocalcet 6 mg 4 times daily. Because of the extremely small number of patients investigated in the Japanese study, information on the safety and efficacy of evocalcet 6 mg 4 times daily should be collected continuously in the post-marketing surveillance, etc.

7.R.6 Post-marketing investigations

The applicant plans to conduct a specified drug use-results survey as shown in Table 14.

Table 14. Outline of the plan for specified drug use-results survey (draft)

Objective	To investigate the safety and efficacy of evocalcet in patients with hypercalcaemia associated with parathyroid carcinoma or intractable PHPT
Survey method	Central registry
Population	Patients with hypercalcaemia associated with parathyroid carcinoma or intractable PHPT
Planned sample size	250
Survey period	4 years (registration period, 2 years)
Observation period	1 year (or until study discontinuation if treatment with evocalcet is discontinued during the observation period)
Main survey items	• Patient characteristics (primary disease, past history, concurrent diseases, etc.) • Use of evocalcet (dose per administration, daily dose frequency, compliance, reason for discontinuation, etc.) • Use of concomitant drugs • Surgical treatment given (e.g., PTx) • Laboratory tests (serum Ca levels, serum iPTH levels, serum phosphate, etc.) • Adverse events (date of onset, seriousness, discontinuation of evocalcet administration or not, outcome, causal relationship to evocalcet, etc.)

In view of the extremely small number of patients investigated in the Japanese study, the surveillance should be conducted covering all patients treated with evocalcet, whenever possible. The following information should be collected in the post-marketing setting:

- Safety and efficacy of evocalcet at the maximum dose of 24 mg
- Incidence of events related to upper gastrointestinal disorder or to hypercalcaemia

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The inspection is currently ongoing. Results and the conclusion of PMDA will be reported in Review Report (2).

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The inspection is currently ongoing. Results and the conclusion of PMDA will be reported in Review Report (2).

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that Orkedia has efficacy in the treatment of hypercalcaemia in patients with parathyroid carcinoma and hypercalcaemia in patients with primary hyperparathyroidism who are unable to undergo parathyroidectomy or patients with recurrent primary hyperparathyroidism after parathyroidectomy, and that Orkedia has acceptable safety in view of its benefits. PMDA has concluded that Orkedia may be approved if Orkedia is not considered to have any particular problems based on comments from the Expert Discussion on the efficacy, safety, indications, dosage and administration, and post-marketing investigation.

Review Report (2)

November 11, 2019

Product Submitted for Approval

Brand Name	Orkedia Tablets 1 mg Orkedia Tablets 2 mg
Non-proprietary Name	Evocalcet
Applicant	Kyowa Kirin Co., Ltd. (formerly Kyowa Hakko Kirin Co., Ltd.)
Date of Application	April 24, 2019

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc., concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc., by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

PMDA's conclusions in Section "7.R.1 Efficacy" described in the Review Report (1) were supported by the expert advisors at the Expert Discussion. The following comments were raised by the expert advisors on the data obtained from patients with parathyroid carcinoma:

- Because parathyroid carcinoma is an extremely rare disease, an extremely limited number of study subjects (i.e., only 3 patients) was unavoidable. Although none of these patients achieved the primary endpoint[6)] regarding corrected serum Ca levels, the corrected serum Ca levels decreased from baseline, suggesting the efficacy of evocalcet. Evocalcet is thus clinically significant in controlling serum Ca levels at the low level, thereby reducing complications associated with hypercalcaemia.

- Because only 3 patients with parathyroid carcinoma were enrolled in the Japanese study, efficacy in each patient should be investigated in detail.

PMDA's view, taking account of the comments raised in the Expert Discussion on the efficacy of evocalcet in patients with parathyroid carcinoma:

Table 15 shows the time course of corrected serum Ca levels in each patient with parathyroid carcinoma enrolled in the Japanese study. In Patient C who discontinued the study at Week 10 due to exacerbation of the primary disease, baseline corrected serum Ca level was 13.6 mg/dL which was the highest among all patients, but decreased to 12.8 mg/dL at Week 8. However, Patient C's corrected

6) Maintained corrected serum Ca levels ≤10.3 mg/dL for 2 weeks during the evaluation period.

serum Ca level increased at Week 10 due to the exacerbation of the primary disease, and the patient did not achieve the secondary endpoint.[7)] On the other hand, in Patient B who discontinued the study at Week 18 because of the occurrence of an adverse event (uterine cancer for which a causal relationship to evocalcet was ruled out), corrected serum Ca levels decreased close to 10.3 mg/dL at both Weeks 10 and 12, achieving the secondary endpoint.[7)] In Patient A who received evocalcet up to Week 52, corrected serum Ca levels were below 10.3 mg/dL at both Weeks 10 and 16, achieving the secondary endpoint.[7)]

Thus, although none of the 3 patients with parathyroid carcinoma achieved the primary endpoint, 2 of 3 patients showed a certain level of decrease in corrected serum Ca levels following treatment with evocalcet. Evocalcet is effective in patients with parathyroid carcinoma, also taking account of the review in Section "7.R.1.4 Efficacy by primary disease."

Table 15. Corrected serum Ca levels in patients with parathyroid carcinoma in the Japanese study

<table>
<tr><td rowspan="2">Evaluation time point (week)</td><td colspan="3">Corrected serum Ca levels (mg/dL)</td></tr>
<tr><td>Patient A</td><td>Patient B</td><td>Patient C</td></tr>
<tr><td>0</td><td>12.8</td><td>11.6</td><td>13.6</td></tr>
<tr><td>2</td><td>12.0</td><td>11.5</td><td>13.8</td></tr>
<tr><td>4</td><td>11.1</td><td>11.2</td><td>13.8</td></tr>
<tr><td>6</td><td>11.1</td><td>11.0</td><td>13.5</td></tr>
<tr><td>8</td><td>11.1</td><td>10.8</td><td>12.8</td></tr>
<tr><td>10</td><td>10.3</td><td>10.4</td><td>13.7</td></tr>
<tr><td>12</td><td>10.6</td><td>10.5</td><td rowspan="13">Study discontinued (exacerbation of primary disease)</td></tr>
<tr><td>14</td><td>10.7</td><td>11.2</td></tr>
<tr><td>16</td><td>10.2</td><td>11.9</td></tr>
<tr><td>18</td><td>10.6</td><td>10.7</td></tr>
<tr><td>20</td><td>10.9</td><td rowspan="12">Study discontinued (adverse events)</td></tr>
<tr><td>22</td><td>11.0</td></tr>
<tr><td>24</td><td>10.6</td></tr>
<tr><td>28</td><td>11.1</td></tr>
<tr><td>32</td><td>10.9</td></tr>
<tr><td>36</td><td>10.4</td></tr>
<tr><td>40</td><td>11.4</td></tr>
<tr><td>44</td><td>11.4</td></tr>
<tr><td>48</td><td>11.0</td></tr>
<tr><td>52</td><td>11.0</td></tr>
</table>

1.2 Safety

PMDA's conclusions in Section "7.R.2. Safety" described in Review Report (1) were supported by the expert advisors at the Expert Discussion.

1.3 Indications, and dosage and administration

PMDA's conclusions in Sections "7.R.4 Indications," and "7.R.5 Dosage and administration" described in the Review Report (1) were supported by the expert advisors at the Expert Discussion. The following comments were raised from the expert advisors on Section "7.R.5 Dosage and administration":

- Since the efficacy and safety of evocalcet were confirmed in the Japanese study, there is no problem in specifying the dosage and administration of evocalcet in line with that employed in the

[7)] Showed a decrease of ≥1.0 mg/dL in corrected serum Ca levels from baseline maintained the reduced level for 2 weeks during the evaluation period.

Japanese study. The use of the increment/decrement of 1 mg per dose allows fine regulation of serum Ca levels depending on the condition of each patient, thus providing a clinical benefit.

- Appropriateness of specifying the maximum dose of evocalcet 6 mg 4 times daily should be confirmed in further detail from the aspect of safety in patients receiving this dosage in the Japanese study.

Taking account of comments raised in the Expert Discussion, PMDA accepted the proposed "Indications" of evocalcet (the treatment of hypercalcaemia associated with parathyroid carcinoma or intractable PHPT).

PMDA's view on the maximum dosage of evocalcet (6 mg 4 time daily):
In the Japanese study, adverse events were observed in 100% (6 of 6) of patients receiving evocalcet 6 mg 4 times daily (nasopharyngitis in 3 patients; sinusitis, tooth fracture, upper respiratory tract infection, atrial fibrillation, back pain, dysgeusia, heat stroke, nephrogenic anaemia, pruritus, spinal compression fracture, faces soft, iron deficiency anaemia, bronchitis, dental caries, gastroenteritis, hordeolum, influenza, eye haemorrhage, pharyngeal haemorrhage, uterine cancer, and chest pain in 1 patient each). All events except for uterine cancer were mild to moderate in severity. The only adverse drug reaction observed was mild dysgeusia in 1 patient. Uterine cancer in 1 patient was the only serious adverse event observed and the only adverse event leading to treatment discontinuation. A causal relationship between the event and evocalcet was ruled out and the outcome was reported as "resolved." Thus, there are no clinically significant problems regarding treatment with evocalcet 6 mg 4 times daily, as judged from the incidences of adverse events. The proposed maximum dosage of evocalcet 6 mg 4 times daily is acceptable, taking account of the reviews presented in Section "7.R.5.3 Maximum dosage."

Based on the above, PMDA instructed the applicant to modify the "Dosage and Administration" of evocalcet for the treatment of hypercalcaemia in patients with parathyroid carcinoma or intractable PHPT and the "Precautions Concerning Dosage and Administration" section of the package insert for the treatment of hypercalcaemia in patients with parathyroid carcinoma or intractable PHPT, as shown below. PMDA confirmed that the applicant responded appropriately.

Indications

○ Hypercalcaemia in patients with any of the following conditions:

- Parathyroid carcinoma
- Primary hyperparathyroidism unable to be treated by parathyroidectomy or recurrent primary hyperparathyroidism after parathyroidectomy

Dosage and Administration

Hypercalcaemia in pateints with parathyroid carcinoma and hypercalcaemia in patients with primary hyperparathyroidism who are unable to undergo parathyroidectomy or patients with recurrent primary hyperparathyroidism after parathyroidectomy:

The usual starting dosage for adults is 2 mg of evocalcet administered orally once daily. The starting dose may be 2 mg twice daily depending on the serum calcium levels of the patient. The subsequent oral dose is adjusted depending on the serum calcium levels of the patient, and may be increased to a maximum of 6 mg 4 times daily.

Precautions Concerning Dosage and Administration

Hypercalcaemia in patients with parathyroid carcinoma and hypercalcaemia in patients with primary hyperparathyroidism who are unable to undergo parathyroidectomy or patients with recurrent primary hyperparathyroidism after parathyroidectomy

1. Serum calcium levels should desirably be measured at the start of treatment with evocalcet, once every 2 weeks before and after dose adjustment, and periodically during the maintenance period.

2. The starting dose of 2 mg twice daily should be considered in patients who have serum calcium levels exceeding 12.5 mg/dL.

3. If necessary, the dose should be adjusted based on the table shown below. The dose should be increased by 1 level at a time at intervals of ≥2 weeks. If serum calcium levels are poorly controlled by the above approach, the dose may be adjusted by an increment/decrement of 1 mg per dose.

Level	Dosage	Daily dose
1	2 mg once daily	2 mg
2	2 mg twice daily	4 mg
3	4 mg twice daily	8 mg
4	6 mg twice daily	12 mg
5	6 mg 3 times daily	18 mg
6	6 mg 4 times daily	24 mg

4. If serum calcium levels have decreased to ≤7.5 mg/dL, treatment should be interrupted immediately. In addition, the use of calcium or vitamin D preparations should be considered, as needed.

5. In case of hypoalbuminaemia (serum albumin level <4.0 g/dL), it is desirable to use a corrected value[Note)] for the index.
   Note) How to calculate corrected calcium level:
   Corrected calcium level (mg/dL) = serum calcium level (mg/dL) – serum albumin level (g/dL) + 4.0

1.4 Risk management plan (draft)

The PMDA's conclusion in Section "7.R.6 Post-marketing investigations" of the Review Report (1) was supported by the expert advisors.

In view of the expert discussion, PMDA has concluded that the risk management plan (draft) for evocalcet should include the safety and efficacy specifications presented in Table 16, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 17 as well as specified use-results surveys presented in Table 18.

Table 16. Safety and efficacy specifications in risk management plan (draft)

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Hypocalcaemia • QT prolongation	• Bone metabolism disorder	• Not applicable
Efficacy specifications		
• Not applicable		

Table 17. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Specified drug use-results survey (patients with SHPT on HD) • Specified drug use-results survey (patients with SHPT on PD) • Early post-marketing phase vigilance (hypercalcaemia) • Specified drug use-results survey (hypercalcaemia)	• Information provision based on the early post-marketing phase vigilance (hypercalcaemia)

Table 18. Outline of the specified use-results survey (draft)

Objective	To investigate the safety and efficacy of evocalcet in patients with hypercalcaemia associated with parathyroid carcinoma or intractable PHPT[a)]
Survey method	All-case surveillance
Population	Patients with hypercalcaemia associated with parathyroid carcinoma or intractable PHPT[a)]
Planned sample size	All treated patients (targets sample size of safety analysis population, 250)
Observation period	1 year (or until study discontinuation if treatment with evocalcet is discontinued during the observation period)
Main survey items	• Patient characteristics (primary disease, past history, concurrent diseases, etc.) • Use of evocalcet (dose per administration, daily dose frequency, compliance, reason for discontinuation, etc.) • Use of concomitant drugs • Surgical treatment given (e.g., PTx) • Laboratory tests (serum Ca levels, serum albumin levels, serum iPTH levels, serum phosphate, etc.) • Adverse events (date of onset, seriousness, discontinuation of evocalcet administration or not, outcome, causal relationship to evocalcet, etc.)

a) Parathyroidectomy-inoperable or postoperative recurrent PHPT

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application document submitted.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that Orkedia may be approved after modifying the indications and dosage and administration as shown below, with the following conditions. Since Orkedia is designated as an orphan drug for the newly added indications, the re-examination period is 10 years.

Indications

○ Secondary hyperparathyroidism in patients on maintenance dialysis
○ Hypercalcaemia in patients with any of the following conditions:
- Parathyroid carcinoma
- Primary hyperparathyroidism unable to be treated by parathyroidectomy or recurrent primary hyperparathyroidism after parathyroidectomy

(Underline denotes additions.)

Dosage and Administration

Secondary hyperparathyroidism in patients on maintenance dialysis

The usual starting dosage for adults is 1 mg of evocalcet administered orally once daily. The starting dose may be 2 mg once daily, depending on the patient's condition. The subsequent oral dose is adjusted within the range from 1 to 8 mg once daily while parathyroid hormone (PTH) and serum calcium levels of the patient are closely monitored. The dose may be increased up to 12 mg once daily if the patient has an inadequate response.

Hypercalcaemia in patients with parathyroid carcinoma and hypercalcaemia in patients with primary hyperparathyroidism who are unable to undergo parathyroidectomy or patients with recurrent primary hyperparathyroidism after parathyroidectomy

The usual starting dosage for adults is 2 mg of evocalcet administered orally once daily. The starting dose may be 2 mg twice daily depending on the serum calcium levels of the patient. The subsequent oral dose is adjusted depending on the serum calcium levels of the patient, and may be increased to a maximum of 6 mg 4 times daily.

(Underline denotes additions.)

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.

2. Since only a limited number of patients participated in clinical studies of the product in Japan, the applicant is required to conduct a post-marketing drug use-results survey involving all patients

treated with the product until data from a specified number of patients have been gathered in order to understand the characteristics of patients treated with the product, and to collect safety and efficacy data as early as possible, so that necessary measures are taken to ensure proper use of the product.

Appendix

List of Abbreviations

Ca	Calcium
Cinacalcet	Cinacalcet hydrochloride
C_{max}	Maximum concentration
Evocalcet	Evocalcet
FAS	Full analysis set
GCP	Good clinical practice
Intractable PHPT	Primary hyperparathyroidism unable to be treated by PTx or recurrent primary hyperparathyroidism after PTx
iPTH	Intact parathyroid hormone
Japanese study	Japanese phase III study on evocalcet in patients with parathyroid carcinoma or intractable PHPT (5.3.5.2-1, Study 7580-101)
LC/MS/MS	Liquid chromatography-tandem mass spectrometry
MedDRA	Medical dictionary for regulatory activities
Orkedia	Orkedia Tablets 1 mg and Orkedia Tablets 2 mg
PHPT	Primary hyperparathyroidism
PMDA	Pharmaceuticals and Medical Device Agency
PTH	Parathyroid hormone
PTx	Parathyroidectomy
SHPT	Secondary hyperparathyroidism
t_{max}	Time to reach maximum concentration