Report on the Deliberation Results

December 2, 2016

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

Brand Name	Cymbalta Capsules 20 mg
	Cymbalta Capsules 30 mg
Non-proprietary Name	Duloxetine Hydrochloride (JAN*)
Applicant	Shionogi & Co., Ltd.
Date of Application	February 9, 2016

Results of Deliberation

In the meeting held on November 25, 2016, the First Committee on New Drugs concluded that the proposed partial changes 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 4 years.

Conditions of Approval

The applicant is required to compile a risk management plan and to implement it properly.

** Japanese Accepted Name (modified INN)*

Review Report

November 15, 2016
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	Cymbalta Capsules 20 mg Cymbalta Capsules 30 mg
Non-proprietary Name	Duloxetine Hydrochloride
Applicant	Shionogi & Co., Ltd.
Date of Application	February 9, 2016
Dosage Form/Strength	Each Capsule contains 22.4 mg of duloxetine hydrochloride (20 mg of duloxetine) or 33.7 mg of duloxetine hydrochloride (30 mg of duloxetine).
Application Classification	Prescription drug, (4) Drug with a new indication
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug III

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of pain associated with osteoarthritis and that the product has acceptable safety in view of its observed benefits (see Attachment).

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

Indications

○ Major depressive disorder

○ Pain associated with the following diseases:

Diabetic neuropathy

Fibromyalgia

Chronic low back pain[1]

Osteoarthritis

(Underline denotes additions)

Dosage and Administration

1. Major depressive disorder

Pain associated with diabetic neuropathy

The usual adult dosage is 40 mg of duloxetine administered orally once daily after breakfast. The starting dose is 20 mg/day. The dose should be escalated by 20 mg/day at intervals of at least 1 week.

The dose may be increased to up to 60 mg/day in patients with inadequate response to the dose of 40 mg/day.

2. Pain associated with fibromyalgia

Pain in associated chronic low back pain

Pain associated with osteoarthritis

The usual adult dosage is 60 mg of duloxetine administered orally once daily after breakfast. The starting dose is 20 mg/day. The dose should be escalated by 20 mg at intervals of at least 1 week.

(Underline denotes additions)

Condition of Approval

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

1 After the submission of this application, the product was approved for the indication "pain associated with chronic low back pain" on March 18, 2016.

Appendix

Review Report (1)

September 21, 2016

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	Cymbalta Capsules 20 mg Cymbalta Capsules 30 mg
Non-proprietary Name	Duloxetine Hydrochloride
Applicant	Shionogi & Co., Ltd.
Date of Application	February 9, 2016
Dosage Form/Strength	Each capsule contains 22.4 mg of duloxetine hydrochloride (20 mg of duloxetine) or 33.7 mg of duloxetine hydrochloride (30 mg of duloxetine).
Proposed Indications	○Major depressive disorder ○ Pain associated with the following diseases: Diabetic neuropathy Fibromyalgia <u>Osteoarthritis</u> (Underline denotes additions)
Proposed dosage and Administration	1. Major depressive disorder Pain associated with diabetic neuropathy The usual adult dosage is 40 mg of duloxetine administered orally once daily after breakfast. The starting dose is 20 mg/day. The dose should be escalated by 20 mg at intervals of at least 1 week. The dose may be increased to up to 60 mg in patients with inadequate response to the dose of 40 mg/day. 2. Pain associated with fibromyalgia <u>Pain associated with osteoarthritis</u> The usual adult dosage is 60 mg of duloxetine administered orally once daily after breakfast. The starting dose is 20 mg/day. The dose should be escalated by 20 mg/day at intervals of at least 1 week. (Underline denotes additions)

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List of Abbreviations

ACR	American College of Rheumatology
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BDI-II	Beck Depression Inventory-II
Bil	Bilirubin
BPI	Brief Pain Inventory
CGI	Clinical Global Impressions
CLBP	Chronic Low Back Pain
CPK	Creatine Phosphokinase
CTD	Common Technical Document
DNP	Diabetic Neuropathic Pain
Duloxetine	Duloxetine Hydrochloride
EMA	European Medicines Agency
FAS	Full Analysis Set
FM	Fibromyalgia
ITT	Intention To Treat
LOCF	Last Observation Carried Forward
MDD	Major depressive disorder
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MMRM	Mixed-effects Model for Repeated Measures
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OA	Osteoarthritis
OC	Observed Case
PGI	Patient Global Impressions of Improvement
PMDA	Pharmaceuticals and Medical Devices Agency
QOL	Quality of Life
SIADH	Syndrome of Inappropriate Secretion of Antidiuretic Hormone
SMQ	Standardized MedDRA Queries
SNRI	Serotonin Noradrenaline Reuptake Inhibitor
SOC	System Organ Class
TG	Triglyceride
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
γ-GTP	γ-glutamyl transpeptidase

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

Duloxetine Hydrochloride (hereinafter referred to as "duloxetine") is a serotonin-noradrenaline reuptake inhibitor (SNRI), and was synthesized at Eli Lilly and Company in the US. In Japan, duloxetine was approved for the treatment of "major depressive disorder " in January 2010, followed by its approvals for the treatment of "pain associated with diabetic neuropathy," "pain associated with fibromyalgia," and "pain associated with chronic low back pain" in February 2012, May 2015, and March 2016, respectively.

Outside Japan, duloxetine has been approved in 100 countries or regions as of July 2016. It has been approved for the treatment of osteoarthritis (OA)-related symptoms (chronic pain or chronic musculoskeletal pain in some countries) in 29 countries or regions, including the US. In Europe, duloxetine has not been approved for OA-related symptoms because of the negative opinion of the European Medicines Agency (EMA) on the benefit and risk of duloxetine in the treatment of "chronic somatic pain," including pain associated with OA [for more details, see Section 7.R.6].

Clinical studies were started in October 2014 as part of the clinical development of duloxetine for the indication of "pain associated with osteoarthritis" in Japan. The applicant has recently submitted a partial change application, claiming that the efficacy and safety of the product for this indication were confirmed.

The following drugs have been approved for the treatment of "pain associated with osteoarthritis" in Japan: non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, some opioids, intra-articular steroid injection, and intra-articular hyaluronate sodium injection.

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

No data relating to quality are submitted in this application because this is an application for the approval of a new indication.

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

No additional data are submitted in this application because this is an application for the approval of a new indication. The data from secondary pharmacodynamic studies using various pain models (CTD 4.2.1.2-01 to CTD 4.2.1.2-04) were submitted as data relating to non-clinical pharmacology at the time of the initial approval.

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

No additional data are submitted in this application because this is an application for the approval of a new indication. The data relating to non-clinical pharmacokinetics were evaluated at the time of the initial approval.

5. Toxicology and Outline of the Review Conducted by PMDA

No additional data are submitted in this application because this is an application for the approval of a new indication. The data relating to toxicology were evaluated at the time of the initial approval.

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

No additional data are submitted in this application because this is an application for the approval of a new indication. The data relating to biopharmaceutic studies and associated analytical methods, as well as those relating to clinical pharmacology were evaluated at the time of the initial approval.

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

The data from a Japanese phase III study (CTD 5.3.5.1-01, Study V9731) and a Japanese long-term extension study (CTD 5.3.5.2-01 and CTD 5.3.5.2-02, Study V9732) conducted in Japanese patients with OA are submitted as the efficacy and safety evaluation data. In addition, the data from foreign phase III studies (reference CTD 5.3.5.1-02, the HMEP study; reference CTD 5.3.5.1-03, the HMFG study; and reference CTD 5.3.5.1-04, the HMGL study) conducted in foreign patients with OA are submitted as the efficacy and safety reference data.

7.1 Japanese phase III study (CTD 5.3.5.1-01, Study V9731 [October 2014 to June 2015])

A randomized, double-blind, placebo-controlled, parallel-group study was conducted to evaluate the efficacy and safety of duloxetine in patients with idiopathic OA (target sample size, 340 patients; 170 per group) diagnosed according to the American College of Rheumatology (ACR) classification criteria (*Arthritis Rheum.* 1986;29:1039-1049).

This study consisted of 4 phases: a 1- to 2-week run-in phase, a 14-week treatment phase, a 1-week tapering phase, and a 1-week follow-up phase. During the treatment phase, a placebo or duloxetine was orally administered at 60 mg/day (at the starting dose of 20 mg/day, which was escalated by 20 mg/day at 1-week intervals), once daily after breakfast. During the tapering phase, a placebo or duloxetine was to be orally administered at 40 mg/day for the first 3 days and at 20 mg/day for the last 4 days, once daily after breakfast. The use of concomitant analgesics including NSAIDs that had been administered before the start of the study was prohibited in principle.[1]

All of the 354 randomized subjects (176 subjects in the placebo group and 178 subjects in the duloxetine group) were included in the safety analysis, of whom 353 subjects (176 and 177 subjects, respectively) constituted the FAS for efficacy analysis, and the remaining 1 subject (in the duloxetine group) who had not been evaluated for post-treatment efficacy was excluded from safety analysis. A total of 31 subjects (14 and 17 subjects, respectively) were withdrawn from the study during the treatment phase, and the

1 The subjects were allowed to use concomitant analgesics if the following conditions were met: the purpose of administration was rescue treatment or treatment of adverse events; the number of consecutive days of administration was ≤3; the cumulative number of days of administration was ≤20; and the drugs were used within the range of their approved dosage. (Even if these conditions were met, the subjects were prohibited from using the concomitant analgesics from the day before the efficacy evaluation to the completion of evaluation.)

main reasons for withdrawal included adverse events (in 2 and 11 subjects, respectively) and inadequate response or aggravated condition (in 6 and 4 subjects, respectively).

The change from baseline in the Brief Pain Inventory (BPI) pain severity index[2] (average pain) at Week 14 for each treatment group in the FAS, which was the primary endpoint, is shown in Table 1. As shown in the table, a statistically significant difference was observed between the placebo group and the duloxetine group ($P < 0.0001$; by MMRM analysis using treatment group, time point, and treatment group by time point interaction as fixed effects and the baseline BPI pain severity index [average pain] as covariate).

Table 1. The change from baseline in the BPI pain severity index (average pain) at Week 14 (FAS, MMRM)

Treatment group	BPI pain severity index (average pain)[a)]		Change from baseline[b) c)]	Between-group comparison[c)]	
	Baseline	Week 14		Difference in the change between groups[d)]	*p*-value
Placebo	5.06 ± 0.98 (176)	3.14 ± 1.70 (161)	-1.80 ± 0.12	-0.77 [-1.11, -0.43]	<0.0001
Duloxetine	5.03 ± 0.96 (177)	2.44 ± 1.54 (160)	-2.57 ± 0.12		

a) Mean ± standard deviation (SD) (Number of subjects evaluated)
b) Adjusted mean ± standard error (SE)
c) MMRM analysis using treatment group, time point, and treatment group by time point interaction as fixed effects and the baseline BPI pain severity index [average pain] as covariate (covariance structure of error variance, unstructured)
d) Duloxetine versus placebo [99% confidence interval (CI)]

Adverse events (including laboratory abnormalities) were noted in 55.7% (98 of 176 subjects) of the placebo group and 67.4% (120 of 178 subjects) of the duloxetine group. No death was noted. Other serious adverse events were noted in 1 subject in the placebo group (cerebellar tumour) and 1 subject in the duloxetine group (malignant ascites) but the causal relationship to the study drug was ruled out in both cases.

Adverse events (including laboratory abnormalities) whose causal relationships to the study drugs were not ruled out were noted in 14.8% (26 of 176 subjects) of the placebo group and 43.3% (77 of 178 subjects) of the duloxetine group. The main events included somnolence (in 5 subjects in the placebo group and 24 subjects in the duloxetine group), thirst (in 3 and 19 subjects, respectively), constipation (in 3 and 18 subjects, respectively), nausea (in 1 and 17 subjects, respectively), malaise (in 2 and 12 subjects, respectively), and decreased appetite (in 0 and 9 subjects, respectively).

No clinically relevant changes were noted in the vital signs (blood pressure and pulse rate) or electrocardiography findings.

On the basis of the above, the applicant explained that duloxetine 60 mg/day showed efficacy superiority over placebo in Japanese patients with OA and was considered to raise no major safety concerns.

[2] The pain severity was evaluated by each subject on a scale of 0 (no pain) to 10 (pain as bad as you can imagine) at baseline, at Weeks 2, 4, 6, 10, and 14, and at termination of the study for the following 4 items:
・The average pain experienced in last 24 hours (average pain)
・The worst pain experienced in last 24 hours (maximum pain)
・The least pain experienced in last 24 hours (minimum pain)
・The pain experienced right now (current pain)

7.2 Japanese long-term extension study (CTD 5.3.5.2-01 and CTD 5.3.5.2-02, Study V9732 [January 2015 to March 2016])

An open-label, uncontrolled study was conducted to evaluate the long-term safety and efficacy of duloxetine in patients who had completed the 15-week study treatment in a Japanese phase III study (CTD 5.3.5.1-01, Study V9731) or Japanese patients who were newly diagnosed as having OA (target sample size, 90 patients; target number of the subjects who have completed 1-year treatment, 60). The "Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions" (PAB/ED Notification No. 592 dated May 24, 1995, issued by the Evaluation Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare) required the sample size of 100 patients and the duration of exposure of 1 year. However, the target sample size of this study was <100 patients for the following reason: A long-term study for CLBP (CTD 5.3.5.2-01 and CTD 5.3.5.2-03 at the time of regulatory submission for CLBP, Study A3332) had been conducted prior to this study, with the target sample size being 150 and the number of subjects who have completed 1-year treatment being 124, and thus the long-term safety of duloxetine in the treatment of chronic pain in patients with orthopedic diseases was considered to have been demonstrated.

This study consisted of 3 phases: a 50-week treatment phase, a 2-week tapering phase, and a 1-week follow-up phase. During the treatment phase, duloxetine was orally administered at 60 mg/day (at the starting dose of 20 mg/day, which was escalated by 20 mg/day at 1-week intervals), once daily after breakfast. During the tapering phase, duloxetine was orally administered at 40 mg/day in the first week and at 20 mg/day in the second week, once daily after breakfast.

A total of 93 subjects entered the extension study (50 subjects having been assigned to the placebo group in the Japanese phase III study [hereinafter referred to as "placebo/duloxetine subjects"] and 43 subjects having been assigned to the duloxetine group in the Japanese phase III study [hereinafter referred to as "duloxetine/duloxetine subjects"]). All of the 93 treated subjects[3] constituted the FAS for safety and efficacy analyses. A total of 12 subjects (7 placebo/duloxetine subjects and 5 duloxetine/duloxetine subjects) were withdrawn from the study during the treatment phase, and the main reasons of withdrawal included the onset of adverse events in 11 subjects (7 placebo/duloxetine subjects and 4 duloxetine/duloxetine subjects).

The BPI pain severity score (average pain) in the FAS over time, which was the efficacy endpoint, is shown in Table 2.

[3] The enrollment of new subjects had been planned to allow for the possibility that the preceding Japanese phase III study (CTD 5.3.5.1-01, Study V9731) might fail to accumulate cases as scheduled, and that this study might also fail to enroll enough subjects to achieve the target sample size. However, no new subjects were actually enrolled.

Table 2. BPI pain severity score (average pain) over time (FAS, Observed Case)

Treatment group	Baseline[a)]	Week 12	Week 24	Week 36	Week 50	Endpoint
Placebo/duloxetine subjects	3.46 ± 1.84 (50)	1.92 ± 1.57 (49)	1.69 ± 1.34 (48)	1.74 ± 1.54 (47)	1.86 ± 1.73 (43)	1.94 ± 1.75 (50)
Duloxetine/duloxetine subjects	2.56 ± 1.53 (43)	1.59 ± 1.18 (41)	1.26 ± 1.21 (39)	1.33 ± 1.11 (39)	1.13 ± 1.21 (38)	1.21 ± 1.30 (43)

Mean ± SD (Number of subjects evaluated)

a) At the start of the long-term extension study (CTD 5.3.5.2-02, Study V9732)

Adverse events (including laboratory abnormalities) were noted in 91.4% (85 of 93 subjects). No case of death was noted. Other serious adverse events were noted in 7 subjects (intervertebral disc protrusion in 2 subjects, and infectious enteritis and loss of consciousness, progressive supranuclear palsy, lumbar spinal stenosis, femur fracture, and intestinal obstruction in 1 subject each), and the causal relationship between the loss of consciousness and the study drug was not denied.

Adverse events (including laboratory abnormalities) whose causal relationships to the study drugs were not ruled out were noted in 51.6% (48 of 93 subjects). The main events included constipation (in 16 subjects), somnolence (in 12 subjects), and thirst (in 11 subjects).

No clinically relevant changes were noted in the vital signs (blood pressure and pulse rate) or electrocardiography (ECG) findings.

On the basis of the above, the applicant considered that the long-term treatment with duloxetine 60 mg/day raised no major safety concerns and that its efficacy was maintained in Japanese patients with OA.

7.R Outline of the Review Conducted by PMDA

7.R.1 Efficacy of duloxetine

7.R.1.1 Subjects of the Japanese phase III study (CTD 5.3.5.1-01, Study V9731)

PMDA asked the applicant to explain the reason why the Japanese phase III study was conducted in patients with idiopathic knee OA, not in patients with OA.

The applicant's explanation:

OA is a chronic degenerative disease of the joint components which is accompanied by reactive bone formation at the joint margins and in the subchondral bones, developing after the deformation, friction, and destruction of the articular cartilage in the limb joints, vertebrae, etc. (*Diagnosis and Treatment of Osteoarthritis.* 2nd ed. Tokyo, Japan: Igaku-Shoin; 2012:6-10. *Biomedicine and therapeutics*. 2010;44:762-765). OA is generally classified as either idiopathic OA, in which no underlying cause is identified, or secondary OA, which is caused by other diseases. The OA pain mechanisms are considered to involve reversible changes in the central nervous system (central sensitization) caused by continuous nociceptive stimulation due to the inflammation in the synovial membrane, changes in subchondral bone, etc., regardless of the presence or absence of underlying diseases or the affected sites (*Bone Joint Nerve*.

2012;2:117-123. *Nat Rev Rheumatol*. 2013;9:654-664). In foreign phase III studies,[4] the most commonly affected site in patients with OA is the knee joint,[5] indicating that the knee is a typical site of lesion in patients with OA. In addition, as the ACR criteria have been widely used as criteria for diagnosis of idiopathic knee OA in clinical and epidemiological studies, the homogeneity of the subjects can be secured. Furthermore, as many clinical studies have been conducted in patients with knee OA, the methods of clinical evaluation have been established. On the basis of the above, the applicant decided that the subjects of the Japanese phase III study should be the patients with idiopathic knee OA diagnosed according to the ACR criteria, taking account of the later comparison of the data with those from a foreign phase III study.

PMDA asked the applicant to explain on what basis the main inclusion criteria for idiopathic knee OA used in the Japanese phase III study (Table 3) were determined.

Table 3. Key inclusion criteria for idiopathic knee OA in the Japanese phase III study

1) Patients with knee OA meeting the following ACR clinical classification criteria for idiopathic osteoarthritis of the knee
・The patient has pain in the knee.
・The presence of osteophytes is confirmed on an X-ray film.
・At least one of the following 3 conditions is met:
a) The age of >50 years
b) Morning stiffness lasting <30 minutes
c) Crepitation produced
2) The patient experienced pain on ≥14 days per months in 3 consecutive months before enrollment.

The applicant's explanation:

In Japan, the diagnostic criteria for idiopathic knee OA have been developed on the basis of the ACR clinical classification criteria etc. (*Diagnosis and Treatment of Osteoarthritis.* 2nd ed. Tokyo, Japan: Igaku-Shoin; 2012:6-10), and the diagnosis is made on the basis of the patient's medical history, clinical symptoms (pain, limited range of motion, contracture, hydrarthrosis, joint deformity), findings from diagnostic imaging (radiography), etc. (*Jpn J Rehabil Med*. 2015;52:256-264). On the other hand, in Japanese and foreign clinical and epidemiological studies, the ACR diagnostic criteria is widely used. The ACR clinical classification criteria for idiopathic knee OA (*Arthritis Rheum.* 1986;29:1039-1049) uses a combination of clinical features and radiographic findings, and the range of the conditions defined as idiopathic knee OA by these criteria is comparable to the range of the conditions diagnosed as idiopathic knee OA in clinical settings in Japan. Therefore, the inclusion criteria regarding OA to be used in the Japanese phase III study were determined with reference to the ACR clinical classification criteria, which had been used in the foreign phase III study, taking account of the later comparison of the data from the Japanese phase III study with those from the foreign phase III study. In addition, in order to exclude the patients with transient or intermittent pain and to include properly the patients with chronic pain, the applicant determined with reference to the condition adopted in the foreign phase III study that the condition as to the duration of pain should be "a patient who experienced pain on ≥14

4 The HMEP study (reference CTD 5.3.5.1-02), the HMFG study (reference CTD 5.3.5.1-03), the HMGL study (reference CTD 5.3.5.1-04).

5 Committee for Development of Japanese Knee OA Guidelines. *OARSI Recommendations for the Management of Knee Osteoarthritis OARSI Evidence-based, Expert Consensus Guidelines*. Adapted version by the Japanese Orthopaedic Association's Committee for Development of Japanese Knee OA Guidelines. http://www.joa.or.jp/member/frame.asp?id1=82 (January 13, 2016).

days per month in 3 consecutive months before enrollment."

PMDA's view:

Because the mechanism of pain in OA is considered to involve reversible changes in the central nervous system (central sensitization) resulting from the persistent stimulation of nociceptors regardless of underlying diseases or affected sites, there should be no major problems with conducting the Japanese phase III study in patients with idiopathic knee OA. In addition, as the clinical methods of diagnosis for idiopathic knee OA in Japan and the ACR clinical classification criteria are comparable, there should be no major problems with the inclusion criteria regarding idiopathic knee OA used in the Japanese phase III study, and thus it is adequate to evaluate the efficacy of duloxetine in Japanese patients with OA using the data from this study. The justification for specifying "pain associated with OA" as an indication of duloxetine will be discussed in Section 7.R.4.

7.R.1.2 Efficacy of duloxetine in the Japanese phase III study

PMDA asked the applicant to explain the clinical significance of the efficacy of duloxetine (the outcome of the primary endpoint) shown in the Japanese phase III study (CTD 5.3.5.1-01, Study V9731) on the basis of the outcomes of other efficacy endpoints.

The applicant's explanation:

The response rates (30% and 50% BPI average pain reduction[6]) (*J Pain*. 2008;9:105-121), which are used as clinically significant indices, at endpoint in the Japanese phase III study are shown in Table 4. Both indices showed more improvement in the duloxetine group than in the placebo group.

Table 4. Response rates (30% and 50% BPI average pain reduction) at endpoint in the Japanese phase III study (FAS)

Treatment group	Number of subjects	Response rate (30% pain reduction)			Response rate (50% pain reduction)		
		Response rate	Relative risk[a)b)]	*p*-value[b)]	Response rate	Relative risk[a)b)]	*p*-value[b)]
Placebo	176	50.0 (88)	1.40 [1.17, 1.67]	0.0001	39.2 (69)	1.64 [1.33, 2.03]	< 0.0001
Duloxetine	177	70.1 (124)			64.4 (114)		

Response rate (%) (Number of responders)

a) Duloxetine versus placebo [95% CI]

b) As estimated by the Mantel-Haenszel method with data stratified according to the BPI pain severity index (average pain) at baseline (<6 vs. ≥6)

Furthermore, the distributions of Patient Global Impression of Improvement (PGI-I)[7] and Clinical Global Impressions of Severity (CGI-S) scales,[8] the comprehensive evaluation indices based on the patient's and the physician's impressions, at endpoint in the Japanese phase III study are shown in Table 5 and Table 6, respectively. Both scales showed higher improvement in the duloxetine group than in the placebo group.

6 Percentage of subjects whose BPI pain severity index (average pain) was reduced from baseline by ≥30% or ≥50% at endpoint

7 Index for patients to evaluate the disease improvement comprehensively as compared with the condition before study treatment on a 7-point scale (from 1 [very much better] to 7 [very much worse]).

8 Index for physicians to evaluate the disease severity comprehensively on a 7-point scale (1, absent; 2, minimal; 3, mild; 4, moderate; 5, moderately severe; 6, severe; 7, extreme)

Table 5. PGI-I at endpoint of the Japanese phase III study (FAS)

	PGI-I		
	Placebo (N = 176)	Duloxetine (N = 177)	*p*-value[b)]
Improved[a)]	116 (65.9)	156 (88.1)	< 0.0001
Unchanged[a)]	46 (26.1)	16 (9.0)	
Aggravated[a)]	14 (8.0)	5 (2.8)	

n (response rate or percentage of subjects classified into each category [%])

a) Improved: Very much better, much better, a little better
Unchanged: No change
Aggravated: A little worse, much worse, very much worse

b) Wilcoxon rank sum test

Table 6. CGI-S at endpoint of the Japanese phase III study (FAS)

	CGI-S		
	Placebo (N = 176)	Duloxetine (N = 177)	*p*-value[b)]
Mild[a)]	113 (64.2)	150 (84.7)	< 0.0001
Moderate[a)]	43 (24.4)	21 (11.9)	
Severe[a)]	20 (11.4)	6 (3.4)	

n (response rate or percentage of subjects classified into each category [%])

a) Mild: Absent, minimal, mild
Moderate: Moderate
Severe: Moderately severe, severe, extreme

b) Fisher's exact test for the rate of the subjects with a "mild" condition

In addition, the changes from baseline in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores,[9] which specifically measure the Quality of Life (QOL) in patients with OA, at Week 14 in the Japanese phase III study are shown in Table 7. The total score and all the subscores showed more improvement in the duloxetine group than in the placebo group.

Table 7. Changes from baseline in WOMAC scores at Week 14 in the Japanese phase III study (FAS, MMRM)

WOMAC score	Treatment group	Baseline[a)]	Week 14[a)]	Change from baseline[b)c)]	Comparison with placebo[c)]	
					Difference in the change between groups[d)]	*p*-value
Total score	Placebo	32.70 ± 13.71 (176)	21.40 ± 14.83 (161)	-10.45 ± 0.91	-6.96 [-9.50, -4.41]	< 0.0001
	Duloxetine	32.67 ± 13.18 (177)	15.23 ± 11.41 (160)	-17.41 ± 0.91		
Subscale score (pain)	Placebo	7.55 ± 2.74 (176)	4.91 ± 3.15 (161)	-2.43 ± 0.21	-1.55 [-2.14, -0.97]	< 0.0001
	Duloxetine	7.46 ± 2.66 (177)	3.46 ± 2.48 (160)	-3.99 ± 0.21		
Subscale score (stiffness)	Placebo	3.02 ± 1.55 (176)	1.98 ± 1.45 (161)	-0.98 ± 0.09	-0.68 [-0.94, -0.42]	< 0.0001
	Duloxetine	3.01 ± 1.49 (177)	1.38 ± 1.21 (160)	-1.66 ± 0.09		
Subscale score (difficulty in performing daily activities)	Placebo	22.14 ± 10.51 (176)	14.51 ± 10.82 (161)	-7.07 ± 0.66	-4.70 [-6.54, -2.85]	< 0.0001
	Duloxetine	22.20 ± 10.21 (177)	10.39 ± 8.35 (160)	-11.77 ± 0.67		

a) Mean ± SD (Number of subjects evaluated)

b) Adjusted mean ± SE

c) As analyzed by MMRM including treatment, time point, and treatment by time point interaction as fixed effects and baseline score as covariate (covariance structure of the error variance: unstructured)

d) Duloxetine versus placebo [95% CI]

On the basis of the above, the efficacy of duloxetine in patients with OA is considered to have clinical significance because higher improvement was noted in the duloxetine group than in the placebo group not only in the change of BPI pain severity index (average pain), which was the primary endpoint, but also in all other secondary endpoints related to pain and QOL.

PMDA accepts the above explanation and considers that the efficacy of duloxetine in patients with OA has been demonstrated.

9 Index consisting of 24 questions (on pain, stiffness, and difficulty in performing daily activities), each answered on a 5-point scale (from 0 to 4) by patients to evaluate knee function.

7.R.1.3 Factors affecting the efficacy of duloxetine

PMDA asked the applicant to explain the factors affecting the efficacy of duloxetine.

The applicant's explanation:

The results of the subgroup analysis by patient characteristic regarding the change from baseline of BPI pain severity index (average pain) at Week 14 in the Japanese phase III study (CTD 5.3.5.1-01, Study V9731) are shown in Table 8. For each characteristic, no clear difference in the change from baseline was noted between subgroups for either the placebo group or the duloxetine group. These results suggest that the efficacy of duloxetine is unlikely to be affected by any specific patient characteristics.

Table 8. Changes from baseline in BPI pain severity index (average pain) at Week 14 in the Japanese phase III study by patient characteristic (FAS, MMRM)

Patient characteristics	Subgroup	Treatment group	BPI pain severity index (average pain)		Change from baseline[a)b)]	Difference in the change between groups[b)c)]
			Baseline	Week 14		
Sex	Men	Placebo	5.02 ± 0.98 (44)	2.92 ± 1.68 (39)	-1.80 ± 0.24	-0.79 [-1.50, -0.09]
		Duloxetine	4.77 ± 0.91 (35)	2.12 ± 1.34 (33)	-2.59 ± 0.26	
	Women	Placebo	5.07 ± 0.99 (132)	3.21 ± 1.71 (122)	-1.81 ± 0.14	-0.75 [-1.14, -0.36]
		Duloxetine	5.10 ± 0.97 (142)	2.53 ± 1.58 (127)	-2.56 ± 0.14	
Age (years)	<65 years	Placebo	4.97 ± 1.04 (68)	3.08 ± 1.46 (62)	-1.80 ± 0.19	-0.54 [-1.07, -0.01]
		Duloxetine	5.04 ± 1.02 (71)	2.74 ± 1.60 (62)	-2.34 ± 0.19	
	≥65 years	Placebo	5.11 ± 0.95 (108)	3.18 ± 1.84 (99)	-1.81 ± 0.16	-0.91 [-1.35, -0.46]
		Duloxetine	5.03 ± 0.93 (106)	2.26 ± 1.48 (98)	-2.71 ± 0.16	
Body weight (kg)[d)]	<61.2 kg	Placebo	5.05 ± 0.95 (83)	3.03 ± 1.78 (77)	-1.95 ± 0.18	-0.65 [-1.13, -0.17]
		Duloxetine	5.02 ± 0.90 (93)	2.33 ± 1.51 (84)	-2.60 ± 0.17	
	≥61.2 kg	Placebo	5.06 ± 1.02 (93)	3.25 ± 1.63 (84)	-1.67 ± 0.17	-0.87 [-1.36, -0.38]
		Duloxetine	5.05 ± 1.04 (84)	2.57 ± 1.58 (76)	-2.54 ± 0.18	
Duration of illness (years)[d)]	<2.83 years	Placebo	4.96 ± 1.04 (81)	2.91 ± 1.67 (75)	-2.03 ± 0.17	-0.83 [-1.30, -0.37]
		Duloxetine	5.12 ± 1.05 (95)	2.21 ± 1.43 (85)	-2.87 ± 0.16	
	≥2.83 years	Placebo	5.14 ± 0.93 (95)	3.35 ± 1.71 (86)	-1.63 ± 0.17	-0.58 [-1.07, -0.09]
		Duloxetine	4.94 ± 0.85 (82)	2.71 ± 1.63 (75)	-2.22 ± 0.18	
Baseline BPI pain severity index (average pain)[d)]	<5	Placebo	4.00 ± 0.00 (60)	2.73 ± 1.43 (55)	-1.13 ± 0.19	-0.86 [-1.39, -0.34]
		Duloxetine	4.00 ± 0.00 (61)	2.08 ± 1.30 (53)	-2.00 ± 0.19	
	≥5	Placebo	5.60 ± 0.77 (116)	3.36 ± 1.79 (106)	-2.15 ± 0.16	-0.71 [-1.15, -0.28]
		Duloxetine	5.58 ± 0.75 (116)	2.63 ± 1.62 (107)	-2.87 ± 0.16	
Concomitant NSAIDs or acetaminophen[e)]	Used	Placebo group	5.22 ± 1.11 (64)	3.64 ± 1.79 (53)	-1.43 ± 0.22	-0.94 [-1.68, -0.19]
		Duloxetine	5.13 ± 1.07 (32)	2.77 ± 1.68 (30)	-2.36 ± 0.30	
	Not used	Placebo	4.96 ± 0.90 (112)	2.90 ± 1.61 (108)	-2.03 ± 0.15	-0.59 [-0.97, -0.20]
		Duloxetine	5.01 ± 0.94 (145)	2.37 ± 1.51 (130)	-2.61 ± 0.13	

Mean ± SD (Number of subjects evaluated)

a) Adjusted mean ± SE

b) As analyzed by MMRM including treatment, time point, and treatment by time point interaction as fixed effects and the baseline BPI pain severity index (average pain) as covariate (covariance structure of the error variance: unstructured)

c) Duloxetine versus placebo [95% CI]

d) Stratified by the median value

e) Used as a rescue remedy (see1)

PMDA accepts the above explanation, but considers that the impact of the patient characteristics, concomitant drugs, etc. on the efficacy of duloxetine should continuously be investigated via post-marketing surveillance.

7.R.1.4 The impact of the antidepressant effect of duloxetine on the efficacy evaluation

PMDA asked the applicant to explain the impact of the antidepressant effect of duloxetine on the efficacy evaluation.

The applicant's explanation:

Several foreign epidemiological studies have reported the prevalence of depression as a complication in patients with OA is 12.2% to 29%,[10] and thus depression may be included in the complications of OA. On that basis, those with concurrent psychiatric diseases, including depression, have been excluded from the subjects of the Japanese and foreign clinical studies in order to exclude the impact of the antidepressant effect of duloxetine on the efficacy evaluation. The changes from baseline in the BPI pain severity index (average pain) at Week 14 in the Japanese phase III study (CTD 5.3.5.1-01, Study V9731) by baseline Beck Depression Inventory-II (BDI-II) score[11] are shown in Table 9. In the subgroup of the subjects whose BDI-II scores were <14, stronger tendency to improve was noted in the duloxetine group than in the placebo group. This result indicates that duloxetine is effective also in patients without depressive symptoms.

Table 9. Changes from baseline in BPI pain severity index (average pain) at Week 14 in the Japanese phase III study by baseline BDI-II score (FAS, MMRM)

	Subgroup	Treatment group	BPI pain severity index (average pain)		Change from baseline[a)b)]	Difference in the change between groups[b)c)]
			Baseline	Week 14		
Baseline BDI-II score	<14	Placebo	5.05 ± 0.99 (167)	3.17 ± 1.69 (153)	-1.78 ± 0.13	-0.86 [-1.21, -0.51]
		Duloxetine	5.01 ± 0.97 (163)	2.35 ± 1.52 (147)	-2.65 ± 0.13	
	≥14	Placebo	5.11 ± 0.93 (9)	2.63 ± 1.85 (8)	-2.20 ± 0.53	0.44 [-0.98, 1.85]
		Duloxetine	5.36 ± 0.93 (14)	3.46 ± 1.51 (13)	-1.77 ± 0.41	
	14-19	Placebo	5.13 ± 0.99 (8)	3.00 ± 1.63 (7)	-1.68 ± 0.51	-0.48 [-1.94, 0.98]
		Duloxetine	5.10 ± 0.88 (10)	2.90 ± 1.20 (10)	-2.16 ± 0.43	
	20-28	Placebo	5.00 (1)	0 (1)		
		Duloxetine	6.33 ± 0.58 (3)	5.50 ± 0.71 (2)		
	≥29	Placebo	-	-		
		Duloxetine	5.00 (1)	5.00 (1)		

Mean ± SD (Number of subjects evaluated)
-: No subjects fall under this category
a) Adjusted mean ± SE
b) As analyzed by MMRM including treatment, time point, and treatment by time point interaction as fixed effects and the baseline BPI pain severity index (average pain) as covariate (covariance structure of the error variance: unstructured)
c) Duloxetine versus placebo [95% CI]

Although the pain improvement tended to be smaller in the duloxetine group than that in the placebo group within the subgroup of subjects whose baseline BDI-II scores were ≥14, the number of subjects evaluated in this subgroup was limited. Furthermore, in the 1 subject whose baseline BDI-II score was ≥14 and who received a placebo, a marked improvement in the BPI pain severity index at Week 14 as compared to the baseline score was noted. In addition, the final changes in the BPI pain severity index (average pain) by the baseline BDI-II score in foreign phase III studies[12] are shown in Table 10. The pain improvement was not consistently smaller in the duloxetine group than in the placebo group in this

10 *J Med Econ*. 2011;14:497-507. *East Asian Arch Psychiatry.* 2015;25:150-158. *J Gen Intern Med.* 2015;30:1803-1811. *Arthritis.* 2015;2015:327161. *Arthritis Rheum*. 2007;57:415-422.
11 The patient evaluates 21 items about depressive symptoms, including sadness, pessimism, past failure, and loss of pleasure, on a 4-point scale (0 to 3), and the total score (0 to 63) is calculated. The scores of 0 to13, 14 to19, 20 to 28, and 29 to 63 indicate minimal depression, mild depression, moderate depression, and severe depression, respectively.
12 The HMEP study (reference CTD 5.3.5.1-02) and the HMFG study (reference CTD 5.3.5.1-03) in which BD-II scores were collected.

subgroup, although the size of the subgroup of subjects whose BDI-II score was ≥14 was small in either study.

Table 10. Changes from baseline in BPI pain severity index (average pain) in foreign phase III studies by baseline BDI-II score (FAS, MMRM)

	Subgroup	Treatment group	BPI pain severity index (average pain)		Change from baseline[a)b)]	Difference in the change between groups[b)c)]
			Baseline	Week 13		
The HMEP study	<14	Placebo	6.21 ± 1.56 (103)	4.34 ± 2.33 (90)	-1.89 ± 0.23	-1.19 [-1.80, -0.59]
		Duloxetine 60/120 mg[d)]	6.08 ± 1.56 (100)	3.05 ± 2.03 (78)	-3.08 ± 0.23	
	≥14	Placebo	6.31 ± 1.45 (16)	4.92 ± 1.89 (13)	-1.44 ± 0.72	-1.45 [-4.11, 1.21]
		Duloxetine 60/120 mg[d)]	6.91 ± 1.64 (11)	4.38 ± 2.56 (8)	-2.89 ± 0.89	
The HMFG study	<14	Placebo	6.11 ± 1.25 (112)	4.29 ± 1.96 (100)	-1.89 ± 0.20	-0.91 [-1.43, -0.39]
		Duloxetine 60/120 mg[e)]	6.02 ± 1.39 (116)	3.41 ± 1.96 (94)	-2.79 ± 0.21	
	≥14	Placebo group	6.38 ± 1.41 (16)	4.06 ± 2.02 (16)	-1.75 ± 0.45	-0.18 [-1.73, 1.38]
		Duloxetine 60/120 mg[e)]	6.64 ± 1.36 (11)	4.00 ± 1.91 (7)	-1.93 ± 0.68	

Mean ± SD (Number of subjects evaluated)

a) Adjusted mean ± SE

b) As analyzed by MMRM including treatment, the presence or absence of the use of NSAIDs, study site, time point, and treatment by time point interaction as fixed effects, and the baseline score and the baseline score by time point interaction as covariates
(Covariance structure of error variance: Toeplitz [the HMEP study]; heterogeneous Toeplitz [the HMFG study])

c) Duloxetine group−Placebo group [95% CI]

d) Administration of duloxetine was started at 30 mg/day, and the dose was increased to 60 mg/day 1 week after the start of administration. Seven weeks after the start of administration, the subjects were assigned in a 1:1 ratio to duloxetine 60 mg/day or duloxetine 120 mg/day.

e) Administration of duloxetine was started at 30 mg/day, and the dose was increased to 60 mg/day 1 week after the start of administration. Seven weeks after the start of administration, the dose was increased from 60 mg/day to 120 mg/day in the subjects whose BPI pain severity index (average pain) was not reduced by ≥30% from baseline.

The changes in the BPI pain severity index (average pain) at Week 14 by the final change in the BDI-II score in the Japanese phase III study are shown in Table 11. Since the same level of improvement was seen in both the group of subjects whose final change in BDI-II score was <0 and the group of subjects whose final change in BDI-II score was ≥0 in the duloxetine group, the effect of duloxetine to improve pain was considered to be demonstrated regardless of the presence or absence of the improvement in depressive symptoms.

Table 11. Changes in BPI pain severity index (average pain) at Week 14 by the final change in BDI-II score in the Japanese phase III study (FAS, MMRM)

			BPI pain severity index (average pain)		Change from baseline[a)]
			Baseline	Week 14	
Placebo	Overall		5.06 ± 0.98 (176)	3.14 ± 1.70 (161)	-1.80 ± 0.12
	Final change in BDI-II score	<0	5.06 ± 0.82 (66)	2.91 ± 1.64 (65)	-2.16 ± 0.19
		≥0	5.05 ± 1.07 (110)	3.30 ± 1.73 (96)	-1.58 ± 0.16
Duloxetine	Overall		5.03 ± 0.96 (177)	2.44 ± 1.54 (160)	-2.57 ± 0.12
	Final change in BDI-II score	<0	5.01 ± 0.91 (70)	2.42 ± 1.54 (67)	-2.60 ± 0.19
		≥0	5.05 ± 1.00 (107)	2.46 ± 1.55 (93)	-2.55 ± 0.16

Mean ± SD (Number of subjects evaluated)

a) Adjusted mean ± SE
As analyzed by MMRM including treatment, time point, and treatment by time point interaction as fixed effects, and the baseline BPI pain severity index (average pain) as covariate (covariance structure of the error variance: unstructured)

PMDA accepts the above explanation, but considers that the analgesic effect of duloxetine in patients with OA complicated by psychiatric diseases should be investigated via post-marketing surveillance because patients with psychiatric diseases, including depression, were excluded from the Japanese and foreign clinical studies.

7.R.2 Safety of duloxetine

7.R.2.1 Difference between OA and the previously approved indications in the safety of duloxetine

PMDA asked the applicant to explain the difference between OA and the previously approved

indications in the safety of duloxetine.

The applicant's explanation:

The incidence of adverse events reported in Japanese placebo-controlled studies in patients with OA, major depressive disorder (MDD), diabetic neuropathic pain (DNP), fibromyalgia (FM), and chronic low back pain (CLBP)[13] is shown in Table 12. The incidence of adverse events tended to be lower in patients with OA than in patients with MDD or DNP, and were comparable with those in patients with FM or CLBP. No major differences were seen between indications in the incidences of serious adverse events, adverse events leading to treatment discontinuation, and severe adverse events. In addition, no major differences were seen between indications in the incidences of the adverse events developing relatively frequently in patients with OA (nasopharyngitis, somnolence, constipation, thirst, nausea, etc.).

13 OA: Study V9731 (CTD 5.3.5.1-01)
MDD: Pooled data from Study A2027 (CTD 5.3.5.1-17 at the time of regulatory submission for MDD) and Study A203C (CTD 5.3.5.1-02 at the time of regulatory submission for MDD) (Only the data from the duloxetine 60 mg/day groups were used as the data of the subjects receiving duloxetine.)
DNP: Pooled data from Study N0821 (CTD 5.3.5.1-01 at the time of regulatory submission for DNP) and Study N0831 (CTD 5.3.5.1-02 at the time of regulatory submission for DNP) (Only the data from the duloxetine 60 mg/day groups were used as the data of the subjects receiving duloxetine.)
FM: Study V9331 (CTD 5.3.5.1-01 at the time of regulatory submission for FM)
CLBP: Study A3331 (CTD 5.3.5.1-01 at the time of regulatory submission for CLBP)

Table 12. Incidences of adverse events reported in Japanese placebo-controlled studies in patients with OA, MDD, DNP, FM, and CLBP

	OA		MDD		DNP		FM		CLBP	
	Placebo	Duloxetine	Placebo	Duloxetine	Placebo	Duloxetine	Placebo	Duloxetine	Placebo	Duloxetine
N	176	178	156	231	222	141	196	194	224	234
Any adverse events	98 (55.7)	120 (67.4)	122 (78.2)	216 (93.5)	167 (75.2)	120 (85.1)	123 (62.8)	148 (76.3)	135 (60.3)	169 (72.2)
Serious adverse events	1 (0.6)	1 (0.6)	0	6 (2.6)	10 (4.5)	2 (1.4)	1 (0.5)	1 (0.5)	4 (1.8)	4 (1.7)
Adverse events leading to treatment discontinuation	2 (1.1)	11 (6.2)	5 (3.2)	26 (11.3)	15 (6.8)	21 (14.9)	15 (7.7)	15 (7.7)	8 (3.6)	16 (6.8)
Severe adverse events	1 (0.6)	1 (0.6)	0	5 (2.2)	5 (2.3)	1 (0.7)	0	1 (0.5)	1 (0.4)	0
Main events										
Nasopharyngitis	28 (15.9)	27 (15.2)	35 (22.4)	34 (14.7)	32 (14.4)	21 (14.9)	29 (14.8)	26 (13.4)	39 (17.4)	26 (11.1)
Somnolence	6 (3.4)	24 (13.5)	19 (12.2)	70 (30.3)	22 (9.9)	38 (27.0)	21 (10.7)	51 (26.3)	16 (7.1)	45 (19.2)
Constipation	3 (1.7)	19 (10.7)	7 (4.5)	38 (16.5)	15 (6.8)	11 (7.8)	8 (4.1)	29 (14.9)	5 (2.2)	25 (10.7)
Thirst	3 (1.7)	19 (10.7)	6 (3.8)	58 (25.1)	5 (2.3)	7 (5.0)	7 (3.6)	14 (7.2)	0	14 (6.0)
Nausea	1 (0.6)	18 (10.1)	15 (9.6)	88 (38.1)	8 (3.6)	24 (17.0)	9 (4.6)	42 (21.6)	6 (2.7)	21 (9.0)
Malaise	2 (1.1)	12 (6.7)	6 (3.8)	15 (6.5)	6 (2.7)	13 (9.2)	6 (3.1)	9 (4.6)	3 (1.3)	8 (3.4)
Contusion	7 (4.0)	9 (5.1)	0	0	3 (1.4)	3 (2.1)	2 (1.0)	3 (1.5)	7 (3.1)	16 (6.8)
Decreased appetite	1 (0.6)	9 (5.1)	1 (0.6)	30 (13.0)	3 (1.4)	9 (6.4)	1 (0.5)	13 (6.7)	1 (0.4)	10 (4.3)
Increased ALT	1 (0.6)	8 (4.5)	7 (4.5)	16 (6.9)	9 (4.1)	7 (5.0)	0	2 (1.0)	0	4 (1.7)
Increased AST	1 (0.6)	7 (3.9)	4 (2.6)	11 (4.8)	9 (4.1)	9 (6.4)	0	0	0	3 (1.3)
Diarrhoea	1 (0.6)	6 (3.4)	10 (6.4)	24 (10.4)	7 (3.2)	9 (6.4)	7 (3.6)	8 (4.1)	1 (0.4)	9 (3.8)
Vomiting	0	3 (1.7)	2 (1.3)	12 (5.2)	3 (1.4)	8 (5.7)	4 (2.0)	7 (3.6)	0	1 (0.4)
Upper abdominal pain	1 (0.6)	2 (1.1)	10 (6.4)	11 (4.8)	1 (0.5)	3 (2.1)	4 (2.0)	6 (3.1)	2 (0.9)	2 (0.9)
Dizziness	2 (1.1)	2 (1.1)	6 (3.8)	19 (8.2)	2 (0.9)	8 (5.7)	2 (1.0)	11 (5.7)	2 (0.9)	15 (6.4)
Back pain	8 (4.5)	1 (0.6)	12 (7.7)	10 (4.3)	3 (1.4)	2 (1.4)	4 (2.0)	2 (1.0)	2 (0.9)	4 (1.7)
Increased blood CPK	1 (0.6)	1 (0.6)	9 (5.8)	8 (3.5)	8 (3.6)	2 (1.4)	3 (1.5)	3 (1.5)	3 (1.3)	4 (1.7)
Headache	5 (2.8)	1 (0.6)	26 (16.7)	65 (28.1)	9 (4.1)	6 (4.3)	6 (3.1)	9 (4.6)	3 (1.3)	9 (3.8)
Increased blood bilirubin	0	0	11 (7.1)	4 (1.7)	1 (0.5)	0	4 (2.0)	5 (2.6)	1 (0.4)	1 (0.4)
Increased blood triglycerides	0	0	10 (6.4)	11 (4.8)	3 (1.4)	3 (2.1)	2 (1.0)	2 (1.0)	1 (0.4)	0
Increased blood uric acid	1 (0.6)	0	8 (5.1)	5 (2.2)	3 (1.4)	2 (1.4)	0	1 (0.5)	0	0
Increased blood γ-GTP	3 (1.7)	0	3 (1.9)	11 (4.8)	6 (2.7)	9 (6.4)	4 (2.0)	4 (2.1)	1 (0.4)	2 (0.9)
Musculoskeletal stiffness	0	0	8 (5.1)	7 (3.0)	4 (1.8)	1 (0.7)	0	1 (0.5)	1 (0.4)	0

n (%)

The incidence of adverse events reported in Japanese long-term studies in patients with OA, MDD, DNP, FM, and CLBP[14] are shown in Table 13. No major differences were noted between indications in the incidence of all adverse events, serious adverse events, adverse events leading to treatment discontinuation, and severe adverse events. In addition, no major differences were noted between indications in the incidence of the adverse events developing relatively frequently in patients with OA (constipation, nasopharyngitis, somnolence, thirst, etc.).

14 OA: Study V9732 (CTD 5.3.5.2-01 and CTD 5.3.5.2-02)
MDD: Pooled data from Study A203B (CTD 5.3.5.2-01 at the time of regulatory submission for MDD) and Study A203D (CTD 5.3.5.2-02 at the time of regulatory submission for MDD) (Only the data from the duloxetine 60 mg/day groups were used.)
DNP: Pooled data from Study N0822 (CTD 5.3.5.2-01 at the time of regulatory submission for DNP) and Study N0832 (CTD5.3.5.2-02 at the time of regulatory submission for DNP) (Only the data from the duloxetine 60 mg/day groups were used.)
FM: Study V9332 (CTD 5.3.5.2-01 at the time of regulatory submission for FM)
CLBP: Study A3332 (CTD 5.3.5.2-03 at the time of regulatory submission for CLBP)

Table 13. Incidence of adverse events reported in Japanese long-term studies in patients with OA, MDD, DNP, FM, and CLBP

	OA	MDD	DNP	FM	CLBP
N	93	157	266	149	151
Any adverse events	85 (91.4)	154 (98.1)	255 (95.9)	138 (92.6)	130 (86.1)
Serious adverse events	7 (7.5)	3 (1.9)	37 (13.9)	8 (5.4)	8 (5.3)
Adverse events leading to treatment discontinuation	11 (11.8)	21 (13.4)	54 (20.3)	10 (6.7)	16 (10.6)
Severe adverse events	4 (4.3)	0	18 (6.8)	3 (2.0)	4 (2.6)
Main events					
Constipation	18 (19.4)	26 (16.6)	39 (14.7)	27 (18.1)	15 (9.9)
Nasopharyngitis	15 (16.1)	85 (54.1)	76 (28.6)	58 (38.9)	37 (24.5)
Somnolence	12 (12.9)	61 (38.9)	46 (17.3)	34 (22.8)	29 (19.2)
Thirst	11 (11.8)	43 (27.4)	17 (6.4)	11 (7.4)	9 (6.0)
Contusion	8 (8.6)	3 (1.9)	25 (9.4)	6 (4.0)	17 (11.3)
Dizziness	5 (5.4)	20 (12.7)	24 (9.0)	9 (6.0)	8 (5.3)
Nausea	4 (4.3)	61 (38.9)	34 (12.8)	22 (14.8)	16 (10.6)
Headache	2 (2.2)	39 (24.8)	26 (9.8)	8 (5.4)	10 (6.6)
Increased glycosylated haemoglobin	2 (2.2)	0	54 (20.3)	0	0
Diarrhoea	1 (1.1)	25 (15.9)	13 (4.9)	3 (2.0)	4 (2.6)
Increased blood CPK	1 (1.1)	20 (12.7)	26 (9.8)	1 (0.7)	2 (1.3)
Vomiting	1 (1.1)	17 (10.8)	14 (5.3)	4 (2.7)	0
Increased ALT	1 (1.1)	15 (9.6)	27 (10.2)	1 (0.7)	0
Increased blood triglycerides	0	18 (11.5)	20 (7.5)	4 (2.7)	1 (0.7)
Increased blood γ-GTP	0	6 (3.8)	33 (12.4)	7 (4.7)	2 (1.3)

n (%)

PMDA considers that the risk associated with duloxetine in patients with OA does not exceed that in patients with the previously approved indications according to the data available at present. As particular safety considerations for duloxetine, the following will be discussed in the next sections: central nervous system adverse events, impact on body weight, fall/traumatic injury-related adverse events, suicide-related and hostility/aggression-related adverse events, and safety in elderly patients.

7.R.2.2 Central nervous system adverse events

PMDA asked the applicant to explain the incidence of the central nervous system adverse events in patients with OA receiving duloxetine.

The applicant's explanation:

The incidence of central nervous system adverse events[15] reported in Japanese clinical studies conducted in patients with OA (CTD 5.3.5.1-01, Study V9731; CTD 5.3.5.2-02, Study V9732) is shown in Table 14. Most of the events were mild to moderate, and only progressive supranuclear palsy was noted as a severe adverse event (in 1 subject) in the Japanese long-term extension study. As serious adverse events and adverse events leading to treatment discontinuation, loss of consciousness, and progressive supranuclear palsy (in 1 subject each) were noted in the Japanese long-term extension study.

15 Events in MedDRA System Organ Class (SOC) "Nervous system disorders"

Table 14. Incidence of central nervous system adverse events reported in Japanese clinical studies in patients with OA

	Japanese phase III study		Japanese long-term extension study
	Placebo	Duloxetine	
N	176	178	93
Central nervous system adverse events	19 (10.8)	28 (15.7)	30 (32.3)
Main events			
Somnolence	6 (3.4)	24 (13.5)	12 (12.9)
Dizziness	2 (1.1)	2 (1.1)	5 (5.4)
Headache	5 (2.8)	1 (0.6)	2 (2.2)
Sciatica	3 (1.7)	1 (0.6)	3 (3.2)
Hypoaesthesia	1 (0.6)	0	2 (2.2)

n (%)

As for the timing of onset of central nervous system adverse events observed in the Japanese clinical studies conducted in patients with OA, most of the new-onset events developed in the early phase of treatment, within less than 2 weeks of treatment in the Japanese phase III study and within less than 8 weeks in the Japanese long-term extension study. The incidence of central nervous system adverse events reported in Japanese clinical studies[13,14] conducted in patients with the previously approved indications is shown in Table 15. Although the incidence tended to be higher in patients with MDD, no major differences were noted between indications as for the adverse events developing relatively frequently.

Table 15. Incidence of central nervous system adverse events reported in Japanese clinical studies conducted in patients with MDD, DNP, FM, and CLBP

	Japanese placebo-controlled studies								Japanese long-term studies			
	MDD		DNP		FM		CLBP		MDD	DNP	FM	CLBP
Treatment group[a)]	P	DLX	P	DLX	P	DLX	P	DLX	DLX	DLX	DLX	DLX
N	156	231	222	141	196	194	224	234	157	266	149	151
Central nervous system adverse events	46 (29.5)	128 (55.4)	40 (18.0)	51 (36.2)	33 (16.8)	71 (36.6)	22 (9.8)	72 (30.8)	100 (63.7)	111 (41.7)	55 (36.9)	54 (35.8)
Main events												
Somnolence	19 (12.2)	70 (30.3)	22 (9.9)	38 (27.0)	21 (10.7)	51 (26.3)	16 (7.1)	45 (19.2)	61 (38.9)	46 (17.3)	34 (22.8)	29 (19.2)
Headache	26 (16.7)	65 (28.1)	9 (4.1)	6 (4.3)	6 (3.1)	9 (4.6)	3 (1.3)	9 (3.8)	39 (24.8)	26 (9.8)	8 (5.4)	10 (6.6)
Dizziness	6 (3.8)	19 (8.2)	2 (0.9)	8 (5.7)	2 (1.0)	11 (5.7)	2 (0.9)	15 (6.4)	20 (12.7)	24 (9.0)	9 (6.0)	8 (5.3)
Postural dizziness	1 (0.6)	7 (3.0)	0	3 (2.1)	1 (0.5)	2 (1.0)	0	4 (1.7)	5 (3.2)	10 (3.8)	0	5 (3.3)
Disturbance in attention	1 (0.6)	5 (2.2)	0	0	0	0	0	0	1 (0.6)	1 (0.4)	0	0
Dysgeusia	0	3 (1.3)	0	2 (1.4)	0	1 (0.5)	1 (0.4)	1 (0.4)	5 (3.2)	5 (1.9)	2 (1.3)	1 (0.7)
Tremor	0	3 (1.3)	0	2 (1.4)	0	1 (0.5)	0	4 (1.7)	5 (3.2)	4 (1.5)	0	0
Hypoaesthesia	5 (3.2)	2 (0.9)	0	0	0	1 (0.5)	0	1 (0.4)	8 (5.1)	3 (1.1)	2 (1.3)	2 (1.3)
Sciatica	0	0	0	0	0	0	0	1 (0.4)	0	2 (0.8)	1 (0.7)	0

n (%)
a) P: Placebo; DLX: Duloxetine 60 mg/day

On the basis of the above, additional calling for an alert is considered unnecessary because the central nervous system risk of duloxetine in patients with OA does not exceed that in patients with the previously approved indications.

PMDA's view:

Since the incidence of central nervous system adverse events was higher in the duloxetine group than in the placebo group in the Japanese phase III study conducted in patients with OA, sufficient attention should be paid to the onset of these events, somnolence in particular, which was the most frequently seen in the duloxetine group, after administration of duloxetine. Nevertheless, additional calling for an alert against the central nervous system risk is considered unnecessary because most of the central nervous system adverse events noted in the Japanese clinical studies conducted in patients with OA were mild to moderate, and because the risk of duloxetine in patients with OA does not exceed that in patients with the previously approved indications according to the data available at present. The incidences of central nervous system adverse events should continuously be investigated via post-marketing surveillance.

7.R.2.3 Impact on body weight

PMDA asked the applicant to explain the risk for body weight gain associated with duloxetine in patients with OA.

The applicant's explanation:

The changes in body weight over time from the start of treatment with duloxetine in the pooled data from Japanese clinical studies conducted in patients with OA (CTD 5.3.5.1-01, Study V9731; CTD 5.3.5.2-02, Study V9732) are shown in Figure 1. The body weight slightly decreased until Weeks 4 to 6, and showed a tendency toward a gradual increase after Week 15.

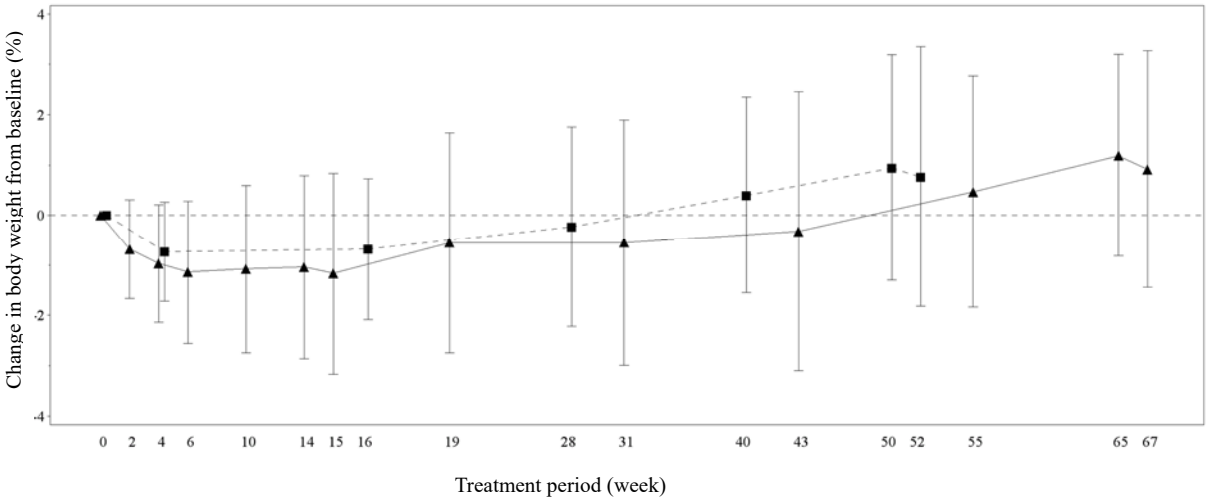

Figure 1. Changes in body weight in the pooled data from Japanese clinical studies conducted in patients with OA (safety analysis population, Observed Case)
(Solid line, duloxetine/duloxetine subjects; Dotted line, placebo/duloxetine subjects; Week 0 refers to the start of treatment)

The numbers of subjects by the change from baseline (the start of treatment) at endpoint in Japanese clinical studies conducted in patients with OA and the previously approved indications[13,14] are shown in Table 16. The percentage of subjects whose body weight increased or decreased by ≥7% did not tend to show major differences between indications.

Table 16. Percentage of subjects by the body weight change from baseline at endpoint reported in Japanese clinical studies

	Japanese placebo-controlled studies										Japanese long-term studies				
	OA		MDD		DNP		FM		CLBP		OA	MDD	DNP	FM	CLBP
Treatment group[a)]	P	DLX	P	DLX	P	DLX	P	DLX	P	DLX	DLX	DLX	DLX	DLX	DLX
N	176	178	151	226	210	127	196	194	224	234	93	157	231	146	151
≤7% decrease	1 (0.6)	6 (3.4)	3 (2.0)	8 (3.5)	4 (1.9)	4 (3.1)	4 (2.0)	12 (6.2)	0	6 (2.6)	1 (1.1)	9 (5.7)	5 (2.2)	3 (2.1)	8 (5.3)
Between >7% and ≤0% decrease	89 (50.6)	129 (72.5)	84 (55.6)	151 (66.8)	100 (47.6)	69 (54.3)	117 (59.7)	129 (66.5)	121 (54.0)	147 (62.8)	28 (30.1)	58 (36.9)	73 (31.6)	45 (30.8)	45 (29.8)
Between >0% and <7% increase	85 (48.3)	42 (23.6)	62 (41.1)	64 (28.3)	99 (47.1)	50 (39.4)	73 (37.2)	51 (26.3)	102 (45.5)	79 (33.8)	54 (58.1)	61 (38.9)	130 (56.3)	71 (48.6)	88 (58.3)
≥7% increase	1 (0.6)	1 (0.6)	2 (1.3)	3 (1.3)	7 (3.3)	4 (3.1)	2 (1.0)	2 (1.0)	1 (0.4)	2 (0.9)	10 (10.8)	29 (18.5)	23 (10.0)	27 (18.5)	10 (6.6)

n (%)

a) P: Placebo; DLX: Duloxetine 60 mg/day

On the basis of the above, no additional calling for an alert in the package insert is considered necessary because the risk for body weight gain is unlikely to increase in patients with OA as compared with those with the previously approved indications.

PMDA's view:

No additional calling for an alert for the risk in patients with OA is considered necessary at present because the incidences of increased body weight and the body weight changes over time reported in the Japanese clinical studies conducted in patients with OA were comparable with those reported in studies conducted in patients with the previously approved indications. However, since a certain number of subjects experienced body weight changes of ≥7% in the long-term extension studies, it is necessary to carefully observe the body weight changes over time during treatment, as well as to call for an alert in the package insert about the onset or aggravation of the underlying diseases and complications and to provide information to healthcare professionals. The body weight changes over time during treatment with duloxetine should continuously be investigated via post-marketing surveillance.

7.R.2.4 Fall/traumatic injury-related adverse events

PMDA asked the applicant to explain the incidence of fall/traumatic injury-related adverse events associated with duloxetine in patients with OA.

The applicant's explanation:

The incidence of fall/traumatic injury-related adverse events[16] reported in Japanese clinical studies conducted in patients with OA (CTD 5.3.5.1-01, Study V9731; CTD 5.3.5.2-02, Study V9732) are shown in Table 17. Most of the events were mild to moderate, and although femur fracture was noted as a severe adverse event (in 1 subject) in the Japanese long-term extension study, its causal relationship to duloxetine was ruled out. In addition, no particular tendency was noted as to the time of onset.

16 Events coded to Standardised MedDRA Query (SMQ) "Accidents and injuries"

Table 17. Incidence of fall/traumatic injury-related adverse events reported in Japanese clinical studies conducted in patients with OA

	Japanese phase III study		Japanese long-term extension study
	Placebo	Duloxetine	
N	176	178	93
Fall/traumatic injury-related adverse events	10 (5.7)	16 (9.0)	22 (23.7)
Main events			
Contusion	7 (4.0)	9 (5.1)	8 (8.6)
Ligament sprain	1 (0.6)	2 (1.1)	6 (6.5)
Chillblains	0	1 (0.6)	0
Muscle injury	0	1 (0.6)	0
Excoriation	0	1 (0.6)	2 (2.2)
Limb-crushing injury	0	1 (0.6)	0
Wound	0	0	2 (2.2)
Frostbite	1 (0.6)	0	1 (1.1)
Animal bite	0	0	1 (1.1)
Cartilage injury	0	0	1 (1.1)
Femur fracture	0	0	1 (1.1)
Foot fracture	0	0	1 (1.1)
Muscle rupture	0	1 (0.6)	1 (1.1)
Rib fracture	0	0	1 (1.1)
Stab wound	0	0	1 (1.1)
Bone contusion	0	0	1 (1.1)
Patella fracture	1 (0.6)	0	0
Comminuted fracture	1 (0.6)	0	0
Thermal burn	1 (0.6)	0	1 (1.1)

n (%)

The incidence of fall/traumatic injury-related adverse events reported in Japanese clinical studies conducted in patients with the previously approved indications[13,14] is shown in Table 18. Although the incidence of all fall/traumatic injury-related adverse events tended to be higher in patients with CLBP, the incidence was comparable with that in patients with OA. Moreover, contusion and ligament sprain were noted in any indications, and no major differences were noted in the tendency of their occurrence between indications.

Table 18. Incidence of fall/traumatic injury-related adverse events reported in Japanese clinical studies conducted in patients with MDD, DNP, FM, and CLBP

	Japanese placebo-controlled studies								Japanese long-term studies			
	MDD		DNP		FM		CLBP		MDD	DNP	FM	CLBP
Treatment group[a)]	P	DLX	P	DLX	P	DLX	P	DLX	DLX	DLX	DLX	DLX
N	156	231	222	141	196	194	224	234	157	266	149	151
Fall/traumatic injury-related adverse events	1 (0.6)	2 (0.9)	10 (4.5)	7 (5.0)	9 (4.6)	6 (3.1)	12 (5.4)	29 (12.4)	7 (4.5)	62 (23.3)	24 (16.1)	44 (29.1)
Main events												
Ligament sprain	0	1 (0.4)	1 (0.5)	1 (0.7)	3 (1.5)	3 (1.5)	1 (0.4)	5 (2.1)	0	7 (2.6)	5 (3.4)	8 (5.3)
Contusion	0	0	3 (1.4)	3 (2.1)	2 (1.0)	3 (1.5)	7 (3.1)	16 (6.8)	3 (1.9)	25 (9.4)	6 (4.0)	17 (11.3)
Cervical nerve root injury	0	0	0	0	0	0	0	2 (0.9)	0	0	0	0
Muscle strain	0	0	2 (0.9)	1 (0.7)	0	0	0	0	0	3 (1.1)	0	1 (0.7)
Thermal burn	0	0	2 (0.9)	0	2 (1.0)	0	0	1 (0.4)	1 (0.6)	7 (2.6)	0	2 (1.3)
Hand fracture	0	0	0	0	1 (0.5)	0	0	0	1 (0.6)	0	0	2 (1.3)
Excoriation	0	0	1 (0.5)	0	1 (0.5)	0	0	1 (0.4)	0	7 (2.6)	0	2 (1.3)
Wound	0	0	1 (0.5)	1 (0.7)	1 (0.5)	0	1 (0.4)	0	0	10 (3.8)	2 (1.3)	4 (2.6)
Foot fracture	0	0	0	0	0	0	0	0	0	3 (1.1)	0	0
Rib fracture	0	0	0	1 (0.7)	0	0	1 (0.4)	1 (0.4)	0	8 (3.0)	1 (0.7)	2 (1.3)
Bone contusion	0	0	0	0	0	0	0	1 (0.4)	0	0	0	4 (2.6)
Chillblains	0	0	0	0	0	0	0	1 (0.4)	0	2 (0.8)	2 (1.3)	0
Fall	0	1 (0.4)	0	1 (0.7)	0	0	0	1 (0.4)	0	2 (0.8)	1 (0.7)	0
Laceration	0	0	0	0	0	0	1 (0.4)	1 (0.4)	0	2 (0.8)	0	1 (0.7)
Scratch	0	0	1 (0.5)	0	0	0	0	0	0	0	2 (1.3)	0
Spinal compression fracture	0	0	0	0	0	0	0	1 (0.4)	0	2 (0.8)	0	1 (0.7)
Thoracic vertebral fracture	0	0	0	0	0	0	0	0	0	2 (0.8)	1 (0.7)	0
Skin abrasion	0	0	0	0	0	0	0	0	0	2 (0.8)	0	0

n (%)

a) P: Placebo; DLX: Duloxetine 60 mg/day

The results of the subgroup analysis of the incidence of fall/traumatic injury-related adverse events by age and by the presence or absence of onset of central nervous system adverse events ware shown in Table 19. The incidence tended to be higher in the subgroup of subjects aged ≥65 years and the subgroup of subjects who had experienced central nervous system adverse events. In the Japanese phase III study, the incidence of fall/traumatic injury-related adverse events in the duloxetine group was higher than that in the placebo group in the subgroup of subjects aged ≥65 years, while a similar tendency was not noted in the subgroup of subjects aged <65 years.

Table 19. Incidence of fall/traumatic injury-related adverse events by age and by the presence or absence of onset of a central nervous system adverse event reported in Japanese clinical studies conducted in patients with OA

		Japanese phase III study		Japanese long-term extension study
		Placebo	Duloxetine	
Age	<65 years	3/68 (4.4)	2/72 (2.8)	7/35 (20.0)
	≥65 years	7/108 (6.5)	14/106 (13.2)	15/58 (25.9)
Onset of a central nervous system adverse event	Observed	1/19 (5.3)	6/28 (21.4)	9/30 (30.0)
	Not Observed	9/157 (5.7)	10/150 (6.7)	13/63 (20.6)

n/N (%)

It is difficult to draw any conclusion about the causal relationship between age and the onset of fall/traumatic injury-related adverse events after duloxetine administration because it has been reported that age as well as severe OA and knee pain are the risk factors of fall (*Japanese Journal of Geriatrics*. 2006;43:92-101. *Clinical Calcium*. 2014;24:679-84). In the Japanese phase III study, the incidence of fall/traumatic injury-related adverse events was comparable between the groups of subjects who had or had not experienced a central nervous system adverse event in the placebo group, whereas the incidence of fall/traumatic injury-related adverse events was higher in the group of subjects who had experienced a central nervous system adverse event in the duloxetine group, and no major differences were noted in the patient characteristics between the groups of subjects who had or had not experienced a central nervous system adverse event. However, it was difficult to conclude at present that the onset of a central nervous system adverse event is a risk factor for the onset of a fall/traumatic injury-related adverse event for the following reason: of 6 subjects of the Japanese phase III study and 9 subjects of the Japanese long-term extension study who experienced both central nervous system and fall/traumatic injury-related adverse events, 5 and 1, respectively, experienced these events around the same time; however, all of the fall/traumatic injury-related adverse events, including stumbling on a step due to carelessness etc. and slipping down during snow-removal work, were considered unrelated to the central nervous system adverse events. On the basis of the above, additional calling for an alert about the administration of duloxetine in patients with OA is considered unnecessary because the risk for fall/traumatic injury-related adverse events in patients receiving duloxetine for treatment of OA is considered comparable with that in patients receiving duloxetine for treatment of the previously approved indications and an alert for this risk has already been called for in the package insert.

PMDA's view:

The results of the Japanese clinical studies conducted in patients with OA have shown that the risk for fall/traumatic injury-related adverse events in patients with OA is unlikely to evidently exceed that in patients with the previously approved indications. However, as advanced age, severe OA, and knee pain are included in the risk factors for fall, attention should be paid to the onset of fall/traumatic injury-related adverse events when administering duloxetine. On the basis of the above, the possibility that the risk for fall or traumatic injury might increase in patients with OA cannot be ruled out. Therefore, it is necessary to continue calling for an alert in the package insert against the risk for central nervous system adverse events and fall/traumatic injury in elderly patients. The incidence of fall/traumatic injury-related adverse events should continuously be investigated via post-marketing surveillance.

7.R.2.5 Suicide-related and hostility/aggression-related adverse events

7.R.2.5.1 Suicide-related adverse events

PMDA asked the applicant to explain the risk for suicide-related adverse events associated with duloxetine in patients with OA.

The applicant's explanation:

As for the incidence of suicide-related adverse events[17] in clinical studies conducted in patients with OA, no suicide-related adverse events were noted in Japanese clinical studies (CTD 5.3.5.1-01, Study V9731; CTD 5.3.5.2-02, Study V9732). In foreign phase III studies,[4] suicidal ideation was noted in 1 of 503 subjects (0.2%) receiving duloxetine, but the event resolved with the discontinuation of the study treatment. In addition, according to the assessment of suicidal risk using the Columbia Suicide Severity Rating Scale in the Japanese clinical studies conducted in patients with OA, no subject experienced suicidal ideation or suicidal behaviour after duloxetine administration.

The incidence of suicide-related adverse events in Japanese clinical studies conducted in patients with the previously approved indications[13,14] was as follows: the incidence in the Japanese placebo-controlled studies was 1.3% (2 of 156 subjects) in the placebo group and 0.9% (2 of 231 subjects) in the duloxetine group in the study conducted in patients with MDD; 0% (0 of 222 subjects) and 0.7% (1 of 141 subjects), respectively, in the duloxetine group in the study conducted in patients with DNP; 0% (0 of 196 subjects) and 0% (0 of 194 subjects), respectively, in the study conducted in patients with FM; and 0% (0 of 224 subjects) and 0% (0 of 234 subjects), respectively, in the study conducted in patients with CLBP. The incidence in the duloxetine groups of the Japanese long-term studies was 1.9% (3 of 157 subjects) in the study conducted in patients with MDD; 0.4% (1 of 266 subjects) in the study conducted in patients with DNP; 0.7% (1 of 149 subjects) in the study conducted in patients with FM; and 0% (0 of 151 subjects) in the study conducted in patients with CLBP. According to the above, suicide-related adverse events associated with the use of duloxetine did not tend to be clearly higher in patients with OA than in patients with the previously approved indications.

In addition, 4808 cases of suicide-related adverse events have been reported as part of the foreign post-marketing safety information of duloxetine,[18] and 12 of them (7 cases of suicidal ideation and 2 cases of suicidal behaviour etc.) involved patients with OA. Although the suicidal risk is difficult to compare between target diseases because the total time of exposure for each disease is unknown, the incidence of adverse events associated with the use of duloxetine in patients with OA did not tend to be clearly higher than that in patients with the previously approved indications.

7.R.2.5.2 Hostility/aggression-related adverse events

PMDA asked the applicant to explain the risk for hostility/aggression-related adverse events associated with duloxetine in patients with OA.

17 Events coded to MedDRA SMQ "Suicide/self-injury"

18 Period of data collection: August 1, 2004 to April 30, 2016. Estimated person-years of exposure: 31,324,000 person-years.

The applicant's explanation:
As for the incidence of hostility/aggression-related adverse events[19] in the clinical studies conducted in patients with OA, no hostility/aggression-related adverse events developed in the subjects of the Japanese phase III study (CTD 5.3.5.1-01, Study V9731). In the Japanese long-term extension study (CTD 5.3.5.2-02, Study V9732), a mild stab wound was noted in 1 subject, but its causal relationship to the study drug was ruled out. In foreign phase III studies,[4] hostility/aggression-related adverse events developed in 0.8% (4 of 508 subjects) in the placebo group and 1.0% (5 of 503 subjects) in the duloxetine group. The most frequently observed events included agitation and laceration.

The incidence of hostility/aggression-related adverse events in Japanese clinical studies conducted in patients with the previously approved indications[13,14] were as follows: the incidences in the Japanese placebo-controlled studies were 0.6% (1 of 156 subjects) in the placebo group and 1.7% (4 of 231 subjects) in the duloxetine group in the study conducted in patients with MDD; 0% (0 of 222 subjects) and 0.7% (1 of 141 subjects), respectively, in the study conducted in patients with DNP; 0% (0 of 196 subjects) and 0% (0 of 194 subjects), respectively, in the study conducted in patients with FM; 0.9% (2 of 224 subjects) and 0.4% (1 of 234 subjects), respectively, in the study conducted in patients with CLBP. The incidences in the duloxetine groups of the Japanese long-term studies were 3.2% (5 of 157 subjects) in the study conducted in patients with MDD; 1.1% (3 of 266 subjects) in the study conducted in patients with DNP; 0.7% (1 of 149 subjects) in the study conducted in patients with FM; and 0.7% (1 of 151 subjects) in the study conducted in patients with CLBP. Based on the above, the incidence of hostility/aggression-related adverse events associated with the use of duloxetine did not tend to be clearly higher in patients with OA than in patients with the previously approved indications.

In addition, 6705 cases of hostility/aggression-related adverse events have been reported as part of the foreign post-marketing safety information regarding duloxetine,[18] and 25 of them (7 cases of irritability, 6 cases of anger, 2 cases each of agitation and mania, etc.) occurred in patients with OA. Comparison of the risk of hostility/aggression-related adverse events between indications is difficult because the total time of exposure for each indication is unknown. However, the incidence of adverse events did not tend to be clearly higher in patients with OA than in patients with the previously approved indications.

On the basis of the above, additional calling for an alert about the administration of duloxetine in patients with OA is considered unnecessary because the risk of suicide-related and hostility/aggression-related adverse events associated with duloxetine in patients with OA is considered comparable with that in patients with the previously approved indications, because an alert for this risk has already been called for in the package insert, and because the materials for healthcare professionals or patients have been prepared and distributed to promote the proper use since the approval of CLBP as a new indication and no major problems have been noted as of 4 months after the approval for CLBP [see Section 7.R.8 for

19 Events coded to MedDRA SMQ "Hostility/aggression"

further details].

PMDA's view:
The submitted data have shown that the risk of suicide-related and hostility/aggression-related adverse events in patients with OA is unlikely to evidently exceed that in patients with the previously approved indications. Therefore, the alert for this risk should continuously be called for in the package insert and information should be provided to healthcare professionals. The incidence of these adverse events after the approval of CLBP as a new indication [see Section 7.R.8 for further details] also shows that the risk of suicide-related and hostility/aggression-related adverse events does not tend to increase as the range of patients to administer duloxetine broadened. However, given that depressive symptom is included in the complications of OA and that patients with a suicidal tendency were excluded from the Japanese clinical studies conducted in patients with OA, sufficient information should be communicated to patients and their family members [see Section 7.R.8 for further details] in addition to calling for an alert in the package insert and providing information to medical institutions. The risk of suicide-related and hostility/aggression-related adverse events associated with the use of duloxetine in patients with OA should continuously be investigated via post-marketing surveillance.

7.R.2.6 Safety in elderly patients
PMDA asked the applicant to explain the safety of duloxetine in elderly patients.

The applicant's explanation:
Idiopathic OA gradually develops in middle-aged and elderly persons aged ≥40 years, and its incidence increases as the age advances (*Diagnosis and Treatment of Osteoarthritis.* 2nd ed. Tokyo, Japan: Igaku-Shoin; 2012:6-10). On the other hand, the age group to which a patient with secondary (idiopathic) OA belongs depends on the onset time of the underlying disease, and thus secondary OA tends to develop at younger ages than idiopathic OA, which is caused by advanced age and other factors.

The incidence of adverse events by age reported in Japanese clinical studies (CTD 5.3.5.1-01, Study V9731; CTD 5.3.5.2-02, Study V9732) is shown in Table 20. No major differences in the incidence of adverse events were noted between subgroups in the Japanese clinical studies, and no particular adverse events tended to occur more frequently depending on age. The incidences of serious adverse events and adverse events leading to treatment discontinuation reported in the foreign phase III studies were as follows: the incidence of serious adverse events were 1.5% (5 of 336 subjects) in the placebo group and 0.6% (2 of 310 subjects) in the duloxetine group among subjects aged <65 years, and 1.2% (2 of 172 subjects) in the placebo group and 3.1% (6 of 193 subjects) in the duloxetine group among subjects aged ≥65 years; and the incidence of adverse events leading to treatment discontinuation was 6.5% (22 of 336 subjects) in the placebo group and 12.9% (40 of 310 subjects) in the duloxetine group among subjects aged <65 years, and 7.6% (13 of 172 subjects) in the placebo group and 20.2% (39 of 193 subjects) in the duloxetine group among subjects aged ≥65 years. There were no major differences between subgroups.

Table 20. Incidence of the main adverse events by age reported in Japanese clinical studies conducted in patients with OA

	<65 years			≥65 years		
	Japanese phase III study		Japanese long-term extension study	Japanese phase III study		Japanese long-term extension study
	Placebo	Duloxetine		Placebo	Duloxetine	
N	68	72	35	108	106	58
Any adverse event	39 (57.4)	47 (65.3)	32 (91.4)	59 (54.6)	73 (68.9)	53 (91.4)
Serious adverse events	0	1 (1.4)	2 (5.7)	1 (0.9)	0	5 (8.6)
Adverse events leading to treatment discontinuation	0	6 (8.3)	5 (14.3)	2 (1.9)	5 (4.7)	6 (10.3)
Severe adverse events	0	1 (1.4)	1 (2.9)	1 (0.9)	0	3 (5.2)
Main events						
Nasopharyngitis	16 (23.5)	12 (16.7)	4 (11.4)	12 (11.1)	15 (14.2)	11 (19.0)
Thirst	0	4 (5.6)	2 (5.7)	3 (2.8)	15 (14.2)	9 (15.5)
Somnolence	2 (2.9)	12 (16.7)	5 (14.3)	4 (3.7)	12 (11.3)	7 (12.1)
Constipation	1 (1.5)	8 (11.1)	6 (17.1)	2 (1.9)	11 (10.4)	12 (20.7)
Nausea	1 (1.5)	9 (12.5)	1 (2.9)	0	9 (8.5)	3 (5.2)
Contusion	2 (2.9)	1 (1.4)	3 (8.6)	5 (4.6)	8 (7.5)	5 (8.6)
ALT increased	0	0	0	1 (0.9)	8 (7.5)	1 (1.7)
AST increased	0	0	0	1 (0.9)	7 (6.6)	1 (1.7)
Malaise	1 (1.5)	6 (8.3)	0	1 (0.9)	6 (5.7)	2 (3.4)
Decreased appetite	1 (1.5)	6 (8.3)	0	0	3 (2.8)	0
Muscle spasms	0	0	2 (5.7)	0	2 (1.9)	2 (3.4)
Intervertebral disc protrusion	0	0	2 (5.7)	0	2 (1.9)	1 (1.7)
Ligament sprain	0	1 (1.4)	1 (2.9)	1 (0.9)	1 (0.9)	5 (8.6)
Dizziness	1 (1.5)	1 (1.4)	2 (5.7)	1 (0.9)	1 (0.9)	3 (5.2)
Hypertension	0	0	4 (11.4)	0	1 (0.9)	3 (5.2)
Osteoarthritis	1 (1.5)	0	2 (5.7)	1 (0.9)	1 (0.9)	0
Sciatica	0	0	2 (5.7)	3 (2.8)	1 (0.9)	1 (1.7)
Cough	0	0	0	0	1 (0.9)	5 (8.6)
Oral herpes	0	0	0	0	1 (0.9)	3 (5.2)
Upper respiratory tract inflammation	1 (1.5)	3 (4.2)	1 (2.9)	0	0	3 (5.2)
Back pain	3 (4.4)	1 (1.4)	2 (5.7)	5 (4.6)	0	3 (5.2)
Spinal osteoarthritis	1 (1.5)	1 (1.4)	3 (8.6)	2 (1.9)	0	1 (1.7)
Eczema	0	1 (1.4)	2 (5.7)	0	0	1 (1.7)
Asthma	0	1 (1.4)	1 (2.9)	1 (0.9)	0	3 (5.2)
Pharyngitis	0	1 (1.4)	1 (2.9)	1 (0.9)	0	3 (5.2)
Headache	4 (5.9)	1 (1.4)	0	1 (0.9)	0	2 (3.4)
Bronchitis	2 (2.9)	0	2 (5.7)	1 (0.9)	0	3 (5.2)
Epicondylitis	0	0	2 (5.7)	0	0	0
Herpes zoster	0	0	1 (2.9)	1 (0.9)	0	3 (5.2)
Hyperhidrosis	0	0	2 (5.7)	0	0	0
Lumbar spinal stenosis	0	0	0	1 (0.9)	0	3 (5.2)
Pruritus	0	0	0	0	0	3 (5.2)
Sinusitis	0	0	2 (5.7)	0	0	0

n (%)

PMDA's view:

Since the incidence of adverse events did not tend to increase in the subgroup of subjects aged ≥65 years as compared with the subgroup of subjects aged <65 years in the Japanese clinical studies, the safety in elderly patients is unlikely to pose a major clinical concern. The safety of duloxetine in elderly patients should continuously be investigated via post-marketing surveillance.

7.R.3 Efficacy and safety of the concomitant use of duloxetine with NSAIDs

Given the recommendations of the Japanese and foreign guidelines [see Section 7.R.7], duloxetine is expected to be used in combination with NSAIDs or acetaminophen (hereinafter referred to as "NSAIDs etc.") in patients with OA. PMDA asked the applicant to explain the efficacy and safety of duloxetine

in combination with NSAIDs etc.

The applicant's explanation:

Although concomitant analgesics, including NSAIDs, were basically prohibited in the Japanese phase III study (CTD 5.3.5.1-01, Study V9731),[1] the efficacy and safety of duloxetine in combination with NSAIDs were investigated in patients with inadequate response to NSAIDs in a foreign phase III study (reference data, CTD 5.3.5.1-04, the HMGL study). The difference between treatment groups in the change from baseline in the 24-hour pain severity score (average pain) (weekly mean value) at Week 8, which was the primary endpoint, was −0.91 ($P < 0.001$, as analyzed by MMRM including baseline value, treatment, study site, time point, treatment by time point interaction, and baseline value by time point interaction as explanatory variables), which showed the superiority of duloxetine over placebo. In the Japanese long-term extension study (CTD 5.3.5.2-02, Study V9732), the subjects were allowed to use concomitant NSAIDs etc. The results of the subgroup analysis of the change from baseline in the BPI pain severity score (average pain) at endpoint by the presence or absence of concomitant NSAIDs etc. are shown in Table 21. No major differences in the efficacy of duloxetine were noted depending on the presence or absence of concomitant NSAIDs etc.

Table 21. Changes from baseline in the BPI pain severity score (average pain) at endpoint by the presence or absence of concomitant NSAIDs etc. in the Japanese long-term extension study (FAS, LOCF)

		N	BPI pain severity score (average pain)		Change from baseline
			Baseline [a)]	Endpoint	
Concomitant NSAIDs etc.[b)]	Not used	67	3.90 ± 1.67	1.49 ± 1.51	-2.40 ± 1.87
	Used	26	4.81 ± 1.55	1.88 ± 1.80	-2.92 ± 1.87

Mean ± SD

a) The starting point for analysis was set at the start of the Japanese phase III study for the duloxetine group and at the start of the Japanese long-term extension study for the placebo group in the Japanese phase III study.

b) The subjects who had used NSAIDs or acetaminophen for ≥14 days per month were included in the subgroup of subjects who "used concomitant NSAIDs etc."

The incidence of adverse events by the presence or absence of the concomitant NSAIDs etc. in the Japanese long-term extension study is shown in Table 22. The incidence of all adverse events tended to be higher in the subjects who used concomitant NSAIDs etc. than in those who did not. The following adverse events showed ≥10% differences in incidence between subgroups: thirst, bronchitis, constipation, and spinal osteoarthritis. However, no major differences between subgroups were noted in the incidence of serious adverse events or adverse events leading to treatment discontinuation. Furthermore, on the basis of the safety profiles of NSAIDs etc., the incidences of gastrointestinal adverse events,[20] adverse events related to gastrointestinal haemorrhage,[21] and cardiovascular adverse events[22] were investigated. The incidence of gastrointestinal adverse events tended to be higher in the subgroup of subjects who used concomitant NSAIDs etc. than in those who did not. However, most of the gastrointestinal adverse events were mild to moderate, and intestinal obstruction was reported in 1 subject as a serious adverse event leading to treatment discontinuation. The causal relationship between duloxetine and the event was ruled out.

20 Events coded to MedDRA SOC "Gastrointestinal disorders"
21 Events coded to MedDRA SMQ "Gastrointestinal haemorrhage"
22 Events coded to MedDRA SMQ "Arrhythmia," "Cardiac failure," "Cerebrovascular disorders," "Ischaemic heart disease," or "Torsade de pointes/QT prolongation"

Table 22. Incidence of adverse events by the presence or absence of concomitant NSAIDs etc. in the Japanese long-term extension study

	Concomitant NSAIDs etc.[a)]	
	Not used	Used
N	67	26
Adverse events	59 (88.1)	26 (100.0)
Serious adverse events	6 (9.0)	1 (3.8)
Adverse events leading to treatment discontinuation	9 (13.4)	2 (7.7)
Severe adverse events	3 (4.5)	1 (3.8)
Gastrointestinal adverse events	18 (26.9)	12 (46.2)
Adverse events related to gastrointestinal haemorrhage	0	0
Cardiovascular adverse events	8 (11.9)	2 (7.7)
Main events		
Constipation	11 (16.4)	7 (26.9)
Thirst	5 (7.5)	6 (23.1)
Bronchitis	1 (1.5)	4 (15.4)
Nasopharyngitis	12 (17.9)	3 (11.5)
Somnolence	9 (13.4)	3 (11.5)
Spinal osteoarthritis	1 (1.5)	3 (11.5)

n (%)

a) The subjects who had used NSAIDs or acetaminophen for ≥14 days per month were included in the subgroup of subjects who "used concomitant NSAIDs etc."

On the basis of the above, duloxetine have a promising efficacy regardless of the presence or absence of concomitant NSAIDs etc., and the use of concomitant NSAIDs etc. is unlikely to increase the risk of adverse events.

PMDA's view:

In light of the submitted data from clinical studies, duloxetine appears to have a promising efficacy regardless of the presence or absence of concomitant NSAIDs etc. Meanwhile, as for the safety of the concomitant use of duloxetine with NSAIDs etc., the possibility that the concomitant use of duloxetine with NSAIDs etc. may increase the risk for adverse events related to gastrointestinal haemorrhage or cardiovascular adverse events cannot be ruled out for the following reasons: because the concomitant use of NSAIDs etc. increased the incidence of gastrointestinal adverse events in the Japanese long-term extension study, although its sample size was small; because duloxetine is known to increase the bleeding tendency when concomitantly used with NSAIDs etc.; and because both duloxetine and NSAIDs have a risk of inducing cardiovascular adverse events. Therefore, an alert for this risk should continuously be called for in the package insert and the risk should continuously be investigated via post-marketing surveillance.

7.R.4 Indications

PMDA asked the applicant to explain the justification for specifying "pain associated with OA" as an indication of duloxetine, although the efficacy and safety of duloxetine was evaluated in patients with idiopathic knee OA in the Japanese phase III study (CTD 5.3.5.1-01, Study V9731).

The applicant's explanation:

The causes of secondary OA are known to include traumatic injury, infection, rheumatoid arthritis, and gout (*Diagnosis and Treatment of Osteoarthritis.* 2nd ed. Tokyo, Japan: Igaku-Shoin; 2012:6-10). In addition, OA develops in the joints of the whole body where the articular cartilage or intervertebral disks exist (*Diagnosis and Treatment of Osteoarthritis.* 2nd ed. Tokyo, Japan: Igaku-Shoin; 2012:110-259). The diagnosis is made on the basis of clinical findings (pain, restricted range of motion, contracture,

hydrarthrosis, joint deformity) and radiographic findings (narrowing of joint space, osteosclerosis in the subchondral bones, osteophyte formation, etc.), and the possibility of secondary OA is examined on the basis of the patient characteristics and the history taken. The mechanisms of onset of pain associated with OA are not considered to vary significantly depending on the presence or absence of the underlying diseases or on the affected sites [see Section 7.R.1.1]. The Japanese and foreign clinical practice guidelines about OA[23] mainly recommend NSAIDs as medications, and the recommended medications do not differ significantly according to the presence or absence of the underlying diseases or to the affected sites. In addition, although no clinical studies have been conducted in patients with secondary OA or with OA of the sites other than the knee, duloxetine is expected to have an analgesic effect irrelevant to the presence or absence of the underlying diseases or to the affected sites, because duloxetine is considered to show an analgesic effect by inhibiting the reuptake of serotonin and noradrenaline, which are involved in the endogenous pain inhibitory mechanisms, via the descending pain inhibitory systems of the brain and the spinal cord and by activating the descending pain inhibitory system. However, the applicant plans to disseminate information about the following point using the materials for proper drug use etc.: the use of anti-inflammatory agents or non-pharmacological therapies should be considered in patients with OA manifesting strong inflammation (crystal-induced arthritis caused by calcium pyrophosphate dihydrate crystal or basic calcium phosphates, transiently increased local inflammatory reaction in the joints caused by traumatic injury etc., concurrent pyogenic arthritis, etc.), although the inflammatory manifestation of OA is considered to be rare except in the acute aggravation phase (*Pain Clinic.* 2013;34:791-799).

PMDA asked the applicant to explain the justification for not limiting the indication of duloxetine to "chronic pain" although the Japanese phase III study was conducted in chronic-phase patients who had had pain for ≥3 months.

The applicant's explanation:
Pain associated with OA is considered to be maintained in the chronic phase by sensitization and reversible changes in the nervous system caused by persistent nociceptive stimulation resulting from the irreversible structural changes of the joints (*Pain Clinic.* 2013;34:791-799). Furthermore, the diagnosis and treatment of OA in general medical practice do not differentiate the acute and chronic phases by the duration of pain associated with OA. Therefore, not limiting the indication of duloxetine to "chronic pain" is considered adequate.

On the basis of the above, specifying "pain associated with OA" as an indication of duloxetine is considered appropriate in light of the analgesic effect of duloxetine, which can be expected regardless of the presence or absence of the underlying diseases or of the affected sites and in light of the current status of the diagnosis and treatment of OA in Japan.

23 Committee for Development of Japanese Knee OA Guidelines. *OARSI Recommendations for the Management of Knee Osteoarthritis OARSI Evidence-based, Expert Consensus Guidelines*. (Adapted final version by the Japanese Orthopaedic Association's Committee for Development of Japanese Knee OA Guidelines. http://www.joa.or.jp/member/frame.asp?id1=82 [January 13, 2016]). *Osteoarthritis Cartilage*. 2014;22:363-388. *Japanese Hip OA Guidelines*. Tokyo, Japan: Nankodo; 2008:77-90. *J Am Acad Orthop Surg*. 2013;21:571-576. *Arthritis Care Res*. 2012;64:465-474.

PMDA's view:

Considering that the efficacy of duloxetine in the treatment of pain associated with OA can be expected regardless of their underlying diseases or affected sites in view of the OA pain mechanisms and the mechanism of action of duloxetine; and that the diagnosis and treatment of OA do not differentiate the acute and chronic phases by the duration of pain in medical settings; the proposed indication of duloxetine ("pain associated with osteoarthritis") is acceptable. However, it is necessary to provide information about the patient population of the clinical studies to healthcare professionals because the subjects of the clinical studies of duloxetine were limited to patients with idiopathic knee OA, despite the wide variety of the underlying diseases and affected sites in patients with OA. In addition, it is necessary to collect information widely about the safety and efficacy of duloxetine by the presence or absence of underlying diseases, by underlying disease type, and by the affected site, and to rapidly provide this information to healthcare professionals. The final conclusions about the indications of duloxetine should be drawn on the basis of the comments from the expert advisors at the Expert Discussion.

7.R.5 Dosage and administration

PMDA asked the applicant to explain the justification for the proposed dosage and administration, including the grounds for the determination of the dosage and administration in the Japanese phase III study (CTD 5.3.5.1-01, Study V9731).

The applicant's explanation:

The Japanese phase III study was drafted on the assumption that the efficacy of duloxetine could be expected at 60 mg/day in Japanese patients with OA, which was made on the basis of the following points and with reference to the data from foreign clinical studies:

- Of the foreign phase III studies,[4] the HMEP study and the HMFG study showed significant improvement in the respective primary endpoints[24] in the duloxetine 60/120 mg/day group as compared with the placebo group. In the US, duloxetine has been approved for chronic musculoskeletal pain, including OA, at the recommended maintenance dose of 60 mg/day.
- No major differences in the pharmacokinetics have been noted between Japanese and foreigners.
- Both Japanese and foreign clinical studies were conducted in patients with idiopathic knee OA diagnosed according to the ACR clinical classification criteria.
- The safety of duloxetine 60 mg/day has been confirmed in foreign patients with OA and it has also been confirmed in Japan although in patients with other indications.

Although the maintenance dose of duloxetine has been set at 40 mg/day in the dosage and administration approved for the indications of MDD and DNP in Japan, the risk for adverse events associated with duloxetine 60 mg/day is unlikely to be higher than the risk associated with duloxetine 40 mg/day

24 The primary endpoint of the HMEP study was the change from baseline in the 24-hour pain severity score (average pain) (weekly mean value) evaluated on the 11-point Likert scale recorded in the electronic diary, and that of the HMEP study was the change from baseline in BPI pain severity index (average pain).

according to the following incidences of adverse events reported in the Japanese clinical studies conducted in patients with DNP, in which some subjects were assigned to duloxetine 40 mg/day: the incidences of adverse events analyzed with the pooled data from the phase III studies (Study N0821 [CTD 5.3.5.1-01 at the time of regulatory submission for DNP] and Study N0831 [CTD 5.3.5.1-02 at the time of regulatory submission for DNP]) were 75.2% (167 of 222 subjects) in the placebo group, 85.6% (119 of 139 subjects) in the duloxetine 40 mg/day group, and 85.1% (120 of 141 subjects) in the duloxetine 60 mg/day group; and the incidences of adverse events analyzed with data from the long-term extension studies (Study N0822 [CTD 5.3.5.2-01 at the time of regulatory submission for DNP] and Study N0832 [CTD 5.3.5.2-02 at the time of regulatory submission for DNP]) were 97.9% (138 of 141 subjects) in the duloxetine 40 mg/day group and 95.9% (255 of 266 subjects) in the duloxetine 60 mg/day group. In addition, neither Japanese nor foreign studies have ever evaluated the efficacy and safety of duloxetine administered at the maintenance dose of 40 mg/day in patients with OA. Therefore, the Japanese phase III study in patients with OA involved no treatment with duloxetine at the maintenance dose of 40 mg/day but only adopted the maintenance dose of 60 mg/day at which the efficacy and safety of duloxetine had already been established overseas. Setting the maintenance dose of duloxetine at 60 mg/day in Japanese patients with OA is considered appropriate because clinically significant improvement was observed in the duloxetine 60 mg/day groups of the Japanese clinical studies (CTD 5.3.5.1-01, Study V9731; CTD 5.3.5.2-02, Study V9732) [see Section 7.R.1.2] while no major safety concerns were noted [see Section 7.R.2].

The dose escalation method in the Japanese phase III study conducted in patients with OA was set as follows, because a favorable tolerability after the start of duloxetine administration had been confirmed at the initial dose of 20 mg/day in the Japanese phase III studies conducted for the indication of MDD:[13] duloxetine was administered at the initial dose of 20 mg/day for 1 week and the dose was then escalated by 20 mg/day at intervals of 1 week up to 60 mg/day. Discontinuation due to adverse events during the first week of treatment occurred in 0 of 176 subjects in the placebo group and 3 of 178 subjects (1.7%) in the duloxetine group, which showed no major difference between treatment groups. On the basis of the above, duloxetine should be administered to Japanese patients with OA at the initial dose of 20 mg/day for 1 week and then the dose should be escalated by 20 mg/day at intervals of at least 1 week.

PMDA accepts the above explanation and considers that there should be no major problems in the dosage and administration proposed for the indication of OA.

7.R.6 Situation of reviews in foreign countries etc.

While the supplemental application for the indication of chronic musculoskeletal pain was approved in the US, the addition of the indication of chronic somatic pain was refused in Europe. Despite the EMA's refusal, the applicant decided to submit an application for the addition of a new indication in Japan. PMDA asked the applicant to explain why such decision was made on the basis of the data from Japanese clinical studies.

The applicant's explanation:

In the US, on the one hand, duloxetine was approved for the indication of "chronic musculoskeletal pain" in November 2010 on the basis of the data from phase III studies conducted in patients with OA (reference data, CTD 5.3.5.1-02, the HMEP study; reference data, CTD 5.3.5.1-03, the HMFG study) and foreign clinical studies conducted in patients with CLBP.[25] In Europe, on the other hand, an extension application was submitted for the indication of "treatment of moderately severe chronic somatic pain" in October 2010 on the basis of the same data from clinical studies as those submitted in the US, but the EMA issued a negative opinion on the application for duloxetine for the treatment of chronic somatic pain, resulting in the refusal of the addition of this indication. The following 5 points were presented in the EMA's opinion: 1) clinical significance of efficacy; 2) durability of effectiveness; 3) safety in patients with the proposed indication; 4) efficacy and safety in elderly patients; and 5) risks and benefits of duloxetine. The details of each point are presented in the sections below.

7.R.6.1 Clinical significance of effectiveness

The EMA presented its negative opinion on the clinical significance of the analgesic effect of duloxetine shown in foreign phase III studies because, although statistically significant differences were noted in the duloxetine groups as compared with the placebo groups, the differences between treatment groups were very small. However, in the Japanese phase III study (CTD 5.3.5.1-01, Study V9731), the effect size of the change in BPI pain severity index (average pain)[26,27] (0.51) was comparable to that in the clinical studies of other therapeutic drugs for OA (0.35-0.63).[28] In addition, higher improvement was noted in the duloxetine group than in the placebo group in terms of the response rates of 30% and 50% BPI average pain reduction, and other secondary endpoints (PGI-I, CGI-S, and WOMAC score) [see Section 7.R.1.2]. On the basis of the above, the differences between treatment groups noted in the Japanese phase III study are considered clinically significant because the efficacy of duloxetine was consistently demonstrated not only in the evaluation of pain severity but also in the evaluation of subjective symptoms and the evaluation based on a QOL scale specific to OA.

7.R.6.2 Durability of effectiveness

The EMA presented its view that the long-term efficacy of duloxetine had not been fully investigated because the number of those who completed the foreign long-term study (reference data, CTD5.3.5.2-02 at the time of regulatory submission for CLBP, the HMEM-Ex study) was small (64.6% [117 of 181 subjects]), which enabled only limited evaluation. However, the number of completers of the Japanese long-term extension study (CTD 5.3.5.2-02, Study V9732) was 87.1% (81 of 93 subjects) and the change in BPI pain severity index (average pain) is shown in Figure 2, which showed the symptom improvement

25 The HMEO study (reference data, CTD 5.3.5.1-02 at the time of regulatory submission for CLBP), the HMEN study (reference data, CTD 5.3.5.1-03 at the time of regulatory submission for CLBP), the HMGC study (reference data, CTD 5.3.5.1-04 at the time of regulatory submission for CLBP), and the HMEN-Ex study (reference data, CTD 5.3.5.2-02 at the time of regulatory submission for CLBP)

26 Calculated by the following formula: (Difference between treatment groups in the change)/(Estimated dispersion of the change)

27 The difference between treatment groups and the number of subjects and SE at evaluation time point of Study V9731 were used.

28 The summary of product application for NORSPAN TAPE 5 mg etc. http://www.pmda.go.jp/drugs/2011/P201100046/index.html (June 8, 2016). The difference between groups, the number of subjects at baseline, and the SE at evaluation time point of Study BUP3801 were used. The summary of product application for TRAMCET Combination Tablets. http://www.pmda.go.jp/drugs/2011/P201100082/index.html (June 8, 2016). The difference between groups and SD of Study JNS013-JPN-04 were used.

maintained from the start of the Japanese long-term extension study to the end of treatment. The secondary endpoints, including PGI-I, also showed the maintained symptom improvement. Therefore, the long-term efficacy of duloxetine in Japanese patients with OA is considered to have been confirmed by the results of the Japanese long-term extension study.

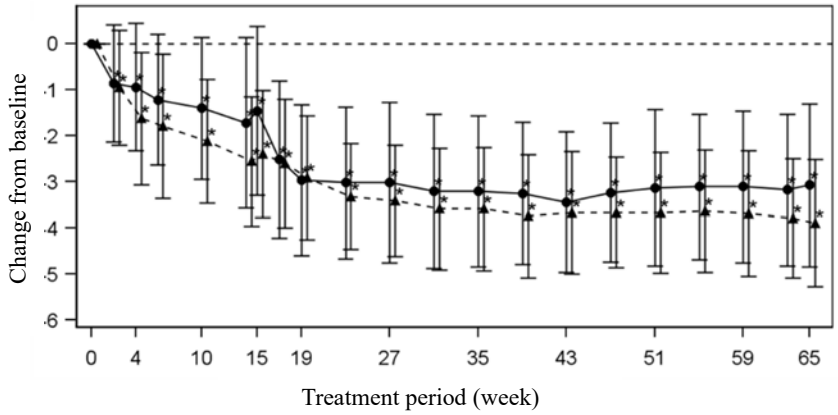

Figure 2. Change (mean ± SD) from baseline over time in BPI pain severity index (average pain) in the Japanese long-term extension study conducted in patients with OA (FAS, Observed Case)
(●: Placebo/duloxetine group; ▲: Duloxetine/duloxetine group; Week 0 refers to the start of treatment in the preceding study)

7.R.6.3 Safety in patients with OA

The EMA presented its view that the safety of the concomitant use of duloxetine with NSAIDs etc., which is anticipated in patients with OA, had not been fully demonstrated. However, in the Japanese long-term extension study, the incidences of all adverse events and gastrointestinal adverse events tended to be higher in the subgroup of subjects who used concomitant NSAIDs etc., but most of them were mild to moderate and the incidences of serious adverse events and adverse events leading to treatment discontinuation did not differ significantly according to the presence or absence of concomitant NSAIDs etc. [see Section 7.R.3]. Therefore, the safety of duloxetine in patients with OA is considered to be comparable to that in patients with the approved indications, although the use of concomitant NSAIDs etc. is anticipated in patients with OA.

7.R.6.4 Efficacy and safety in elderly patients

The EMA presented its view that the efficacy and safety of duloxetine in elderly patients had not been fully demonstrated because the number of elderly subjects enrolled was limited (237 of 839 subjects [28.8%]). However, in the Japanese phase III study, 106 of 178 subjects enrolled (59.6%) were elderly in the duloxetine group, and the change from baseline in the BPI pain severity index (average pain) at Week 14 tended to be higher in the duloxetine group than in the placebo group, even in the subgroup of elderly subjects [see Section 7.R.1.3]. In addition, in Japanese clinical studies (CTD 5.3.5.1-01, Study V9731; CTD 5.3.5.2-02, Study V9732), the incidence of adverse events did not evidently tend to be higher in the subgroups of elderly subjects than those in the subgroups of non-elderly subjects [see Section 7.R.2.6]. Therefore, duloxetine may be used in Japanese patients with OA, including elderly patients, because its efficacy and safety in elderly patients have been confirmed in the Japanese clinical studies.

7.R.6.5 Risk and benefit of duloxetine

The EMA presented its view that the efficacy of duloxetine had not been fully demonstrated, and that the safety profile of duloxetine failed to show a positive risk-benefit balance. However, as explained in the above sections (from Section 7.R.6.1 to Section 7.R.6.4), the data from Japanese clinical studies have demonstrated the efficacy of duloxetine in Japanese patients with OA, and safety is also considered to have no major problems. In addition, taking account of the current status of the pharmacotherapy for OA in Japan, which is unsatisfactory [see Section 7.R.7], the risk-benefit balance of duloxetine in Japanese patients with OA is considered favorable.

PMDA's view:

Despite the EMA's view, the benefit of duloxetine in Japanese patients with OA may not be denied for the following reasons:

- The applicant explained that the difference between treatment groups shown in the Japanese phase III study was clinically significant because the effect size of the change in BPI pain severity index (average pain) in this study was comparable to that in the clinical studies of other therapeutic drugs for OA. However, it is difficult to demonstrate the clinical significance of duloxetine from this comparison because the clinical positioning of duloxetine differs from that of these other therapeutic drugs for OA and the pain severity of the subjects of each study also differs between studies. Nevertheless, the efficacy of duloxetine in Japanese patients with OA is considered clinically significant because consistent improvement was shown not only in terms of the change in the BPI pain severity index (average pain), which was the primary endpoint, but also in terms of the response rates of 30% and 50% BPI average pain reduction, PGI-I, CGI-S, and WOMAC score, which were the secondary endpoints.
- The long-term efficacy of duloxetine is considered to pose no major problems because the improvement from baseline was maintained for approximately 1 year of treatment with duloxetine in the Japanese long-term extension study, although the evaluation was carried out in an open-label, uncontrolled study.
- Although the use of concomitant NSAIDs etc. might increase the risk of adverse events related to gastrointestinal haemorrhage and cardiovascular adverse events, this risk is unlikely to outweigh the benefit as long as an alert is called for in the package insert and information is properly provided to healthcare professionals through information materials etc.
- Duloxetine administration to elderly patients is unlikely to pose major problems for the following reasons: the efficacy of duloxetine in elderly patients can be expected based on the data from the Japanese phase III study; and from the safety viewpoint as well, the risk of adverse events is unlikely to increase in elderly patients as compared with non-elderly patients.

7.R.7 Clinical positioning

PMDA asked the applicant to explain the clinical positioning of duloxetine in pharmacotherapy for OA.

The applicant's explanation:

Conservative therapies, including pharmacotherapy that aims at pain control, physical therapy, and exercise therapy, are performed for the treatment of OA. In case where these conservative therapies do not alleviate the symptoms, surgical therapy is selected (*Jpn J Rehabil Med*. 2015;52:256-264). The Japanese and foreign guidelines for the diagnosis and treatment of OA[23] mainly recommend NSAIDs as medication, and cite acetaminophen, intra-articular steroid or hyaluronate sodium injection, opioids, etc. as other options. Meanwhile, the current status of the pharmacotherapy for OA is considered unsatisfactory for the following reasons:

- NSAIDs are known for their risk of gastrointestinal and cardiovascular disorders and their long-term use should be avoided as much as possible (*THE BONE*. 2013;27:63-70);
- the risk of serious liver disorder associated with the use of acetaminophen increases dose-dependently (see the package inserts of Calonal Tablet 200, Calonal Tablet 300, Calonal Tablet 500 [acetaminophen]);
- the intra-articular steroid injection has been reported to cause steroid arthropathy and pyogenic arthritis, and thus its long-term continuous use should be avoided (*Diagnosis and Treatment of Osteoarthritis.* 2nd ed. Tokyo, Japan: Igaku-Shoin; 2012:101-106);
- some literature has reported that intra-articular hyaluronate sodium injection cannot be recommended because the meta-analysis of foreign clinical studies showed no clinically significant improvement (*J Am Acad Orthop Surg*. 2013;21:571-576); and
- some opioids have been approved for chronic pain in Japan, but their clinical positioning is an option to consider in case there are no other effective therapies or drugs because they have risk of adverse reactions, including constipation, queasy/vomiting, and somnolence, developing in the early stage of administration, as well as for abuse/dependence (Compliance and Narcotics Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare. *Guidance on the proper use of medical narcotics*. 2012:9-12).

On the basis of the above, duloxetine is considered to provide a useful option for the treatment of OA in Japan for the following reasons:(i) the mechanisms of action of duloxetine are different from those of the approved drugs indicated for OA-related conditions; (ii) its risk of gastrointestinal disorder, cardiovascular disorder, liver disorder, etc. is not higher than that of the approved drugs indicated for OA-related conditions; and (iii) the risk of anticipated adverse reactions is manageable through precautions in the package insert and the measures to promote its proper use which have been implemented since the approval of the indication of "pain associated with CLBP."

PMDA's view:

Duloxetine provides a new option for the treatment of OA, but its safety profile is different from that of the conventional therapeutic drugs for OA. The applicant should therefore provide information and call for an alert appropriately so that healthcare professionals, including physicians, can fully understand the

clinical study results and the safety of duloxetine and can use the product properly. The measures to promote the proper use of duloxetine will be discussed in Section 7.R.8.

7.R.8 Measures to promote the proper use of duloxetine

PMDA asked the applicant to explain the measures to promote the proper use of duloxetine, taking account of the potential risk of suicide-related and hostility/aggression-related adverse events involved in the use of antidepressants, including duloxetine.

The applicant's explanation:

The following measures have been implemented to promote the proper use of duloxetine after the approval of duloxetine for the additional indication of pain associated with CLBP, a condition treated in the same departments as OA:

- Materials specifying the properties of duloxetine and the precautions to promote proper use are prepared. At the time of the request for early post-marketing phase vigilance (EPPV), using these materials, physicians and pharmacists are informed of the matters requiring particular attention for the use of duloxetine. The physicians are asked to sign after understanding the information.
- The physicians prescribing duloxetine for pain associated with CLBP are asked to refer patients to psychiatrists or psychosomatic medicine specialists as needed, because cooperation with them is useful in coping with the potential risk of suicide-related and hostility/aggression-related adverse events.
- Leaflets that specify the particularly important points about the properties of duloxetine and the precautions to promote its proper use are prepared and distributed to healthcare professionals.
- Materials are prepared so that not only patients with CLBP but also their family members can have a better understanding of the potential risk involved in the use of duloxetine. Information is communicated to physicians and pharmacists with regard to the necessity for medication counseling to patients and their family members, as well as the details of the counseling. The physicians and pharmacists are asked to inform patients and their family members of the medication.
- Provision of information to promote proper drug use is carried out regularly, not only once immediately after approval or at the time of the first product delivery.
- Briefing and training sessions for physicians are held in cooperation with relevant academic societies in the fields of orthopedics and psychiatry to keep them well informed of the properties and the precautions for proper use of the product.
- Staff members with specialized knowledge are allocated within the office of the applicant to enable the rapid and accurate provision of information about the properties and proper use of the product.

According to the adverse event reporting at 4 months after the start of the EPPV following the approval of the indication of CLBP, a total of 20 cases of suicide-related adverse events were reported, of which 3 cases (2 cases of suicide attempt and 1 case of completed suicide) involved patients with CLBP, 11 cases involved patients with MDD, 5 cases involved patients with unknown indications, and 1 case involved a patient with off-label use. A total of 24 cases of hostility/aggression-related adverse events

were reported, of which 6 cases (2 cases of irritability and 1 case each of aggression, hypomania, personality change, and abnormal behaviour) involved patients with CLBP, 12 cases involved patients with MDD, 1 case involved a patient with DNP, 1 case involved a patient with FM, and 4 cases involved patients with unknown indications. These adverse events showed no clear tendency toward increased incidence after the approval of CLBP as a new indication. The applicant assessed the suicide-related adverse events reported in patients with CLBP. The case of completed suicide was considered unrelated to duloxetine. Although the causal relationship between suicide attempt and duloxetine could not be ruled out, concurrent depression or depressive tendency was noted in both cases and causative factors other than duloxetine could not be ruled out either. The causality to duloxetine was not ruled out in any of the cases of hostility/aggression-related adverse events, but these adverse events were all non-serious. The applicant explained the current status of information provision activities as part of the EPPV. At 4 months post-approval for the indication of CLBP, consent (signature) was obtained from 66.2% of the medical institutions to be informed of the EPPV, while 97.2% of the potential prescriber institutions already received relevant information at that time. This indicates that duloxetine has been prescribed by well-informed physicians in most institutions. In addition, although the number of inquiries to the call center peaked at 1 month post-approval (995 inquiries/month), the number decreased thereafter and no major problems have been noted. As for the early post-marketing phase safety evaluation, monthly discussions with external psychiatric and orthopedic experts have been held to confirm that the incidence of adverse reactions to duloxetine and the current safety measures have posed no problems. On the basis of the above, additional calling for an alert regarding the use of duloxetine in patients with OA is considered unnecessary as long as the current alert in the package insert and the measures to promote proper drug use implemented after the approval of CLBP will be continued.

PMDA's view:

The measures to promote proper drug use presented by the applicant should have no major problems because no major problems have been noted after approval of "pain associated with CLBP" as an additional indication and because the number of physicians prescribing duloxetine is unlikely to increase dramatically after approval of "pain associated with OA," as both patients with CLBP and patients with OA are treated by physicians in the same therapeutic field. However, the final conclusions about the justification for these measures will be drawn on the basis of the comments from the expert advisors at the Expert Discussion.

7.R.9 Post-marketing investigations

In light of the data from the Japanese and foreign clinical studies conducted in patients with OA, the safety information obtained for the approved indications, and other information, PMDA considers that the following events should be investigated via post-marketing surveillance: hepatic dysfunction, oculomucocutaneous syndrome (Stevens-Johnson syndrome), serotonin syndrome, syndrome of inappropriate antidiuretic hormone secretion (SIADH), convulsion/hallucination, anaphylactic reaction, hypertensive crisis, urinary retention, suicidal behaviour/suicidal ideation, neuroleptic malignant syndrome, hostility/aggression, and withdrawal symptom/rebound phenomenon. In addition, PMDA

considers that the following should also be investigated via post-marketing surveillance: the efficacy and safety of duloxetine by the underlying disease causing OA and the affected site, the safety of duloxetine in combination with NSAIDs etc., the efficacy and safety of duloxetine in elderly patients, and the incidence of fall/traumatic disease-related adverse events.

The applicant plans to conduct a specified drug use-results survey in patients with OA as post-marketing surveillance of duloxetine (target sample size, 500 subjects; duration of observation for each subject, 52 weeks).

PMDA considers that the final conclusions on these investigations should be drawn on the basis of the comments from the expert advisors at the Expert Discussion.

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

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

The new drug application data (CTD 5.3.5.1-01, CTD 5.3.5.2-01, CTD 5.3.5.2-02) were subjected to an on-site GCP inspection was conducted in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection revealed that the clinical studies had been conducted in compliance with GCP as a whole. PMDA thus concluded that there should be no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following finding at a study site, although it had no significant impact on the overall evaluation of the studies. PMDA notified the heads of the study site of this finding as the point to be improved:

[Finding requiring corrective action]

Study site:

Deviation from the study protocols (use of the prohibited concomitant medication)

9. Overall Evaluation

On the basis of the submitted data, PMDA has concluded that duloxetine has efficacy in the treatment of pain associated and that duloxetine has acceptable safety in view of its benefits, on the assumption that measures to promote the proper use of the product are taken appropriately. Duloxetine provides a new option for the treatment of OA and has a clinical significance. The indications of duloxetine,

measures to promote the proper drug use, and post-marketing investigations should be further evaluated at the Expert Discussion.

PMDA has concluded that this application may be approved if duloxetine is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

November 15, 2016

Product Submitted for Approval

Brand Name	Cymbalta Capsules 20 mg
	Cymbalta Capsules 30 mg
Non-proprietary Name	Duloxetine Hydrochloride
Applicant	Shionogi & Co., Ltd.
Date of Application	February 9, 2016

1. Contents of the Review

The comments from the Expert Discussion and the subsequent review 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).

At the Expert Discussion, the expert advisors supported PMDA's conclusions on issues presented in Review Report (1).

PMDA also discussed the following points and took actions as necessary.

1.1 Indications

PMDA's conclusion:

The results from Japanese clinical studies (CTD 5.3.5.1-01, Study V9731; CTD 5.3.5.2-01 and CTD 5.3.5.2-02, Study V9732) and foreign phase III studies (reference data, CTD 5.3.5.1-02, the HMEP study; reference data, CTD 5.3.5.1-03, the HMFG study; and reference data, CTD 5.3.5.1-04, the HMGL study) has demonstrated that duloxetine has a promising efficacy in the treatment of OA [see Section 7.R.1 of the Review Report (1)]. This conclusion was supported by the expert advisors.

Taking into account the promising efficacy of duloxetine in the treatment of pain associated with OA regardless of their underlying diseases or affected sites as well as the OA pain mechanisms and the mechanism of action of duloxetine, the proposed indication of duloxetine ("pain associated with osteoarthritis") is adequate [see Section 7.R.4 of the Review Report (1)]. This conclusion was supported by the expert advisors. Meanwhile, the safety profile of duloxetine, unlike those of conventional therapeutic drugs for pain (such as NSAIDs and acetaminophen), involves the potential risk of suicide-related and hostility/aggression-related adverse events. Therefore, PMDA concluded that to prevent easy

use of the product physicians should be advised that the use of the product for treating pain associated with OA should be considered only in patients having the pain for ≥3 months, and decided that the following statement be added to the "Precautions for Indications" section:

[Precautions for Indications]

5. The use of the product for treating pain associated with osteoarthritis should be considered only in patients having the pain for ≥3 months.

1.2 Risk management plan (draft)

In view of the discussions in Sections 7.R.8 and 7.R.9 of the Review Report (1) and the comments from the expert advisors at the Expert Discussion, PMDA has concluded that the current risk management plan (draft) for duloxetine should include the safety and efficacy specifications as shown in Table 23, and that the applicant should conduct the additional pharmacovigilance and risk minimization activities as shown in Table 24. The applicant explained that it would continue implementing the measures to promote the proper use of duloxetine, which were currently implemented for CLBP, even after the indication of OA was added.

Table 23. Safety and efficacy specifications in the risk management plan (draft)

Safety Specification		
Important identified risks	Important potential risks	Important missing information
・ Serotonin syndrome ・ Neuroleptic malignant syndrome ・ Syndrome of inappropriate antidiuretic hormone secretion (SIADH) ・ Convulsion, hallucination ・ Hepatic dysfunction ・ Oculomucocutaneous syndrome (Stevens-Johnson syndrome) ・ Anaphylactic reaction ・ Hypertensive crisis ・ Urinary retention	・ Suicidal behaviour, suicidal ideation ・ Hostility, aggression ・ Withdrawal symptom, rebound phenomenon	・None
Efficacy specification		
・Long-term efficacy of duloxetine in routine clinical practice		

Table 24. Summary of the additional pharmacovigilance activities and risk minimization activities in the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
・Specified drug use-results survey	・Preparation and provision of materials for healthcare professionals ・Preparation and provision of materials for patients ・Safety measures relating to pain associated with CLBP and OA

Based on the above, PMDA instructed the applicant to conduct post-marketing surveillance to investigate the above points.

The applicant explained that it would conduct a specified drug use-results survey in patients with OA as shown in Table 25.

Table 25. Outline of the specified drug use-results survey (draft)

Objective	To evaluate the long-term safety and efficacy of duloxetine in the 52-week treatment of pain associated with OA in clinical settings and to confirm the use of NSAIDs/acetaminophen and hyaluronate sodium products as well as the safety and efficacy of the drugs in combination with duloxetine
Survey method	Central registry system
Patients	Patients with OA-associated pain with no history of duloxetine administration
Duration of observation	52 weeks
Planned sample size	500 subjects (including 300 subjects on concomitant NSAIDs/acetaminophen)
Main survey items	· Patient characteristics (age, sex, site of pain, underlying diseases [in the cases of secondary condition], timing of onset, past history/concurrent conditions, etc.) · Information on administration of duloxetine (dose, reasons for dose change, reasons for discontinuation/termination, presence or absence of withdrawal symptom/rebound phenomenon, etc.) · Information on administration of drugs other than duloxetine for treating pain associated with OA · Incidence of adverse events · Range of motion, radiographic findings, vital signs, body weight, laboratory data · BPI pain severity index, CGI of severity of illness, PGI of improvement, WOMAC, BDI-II

PMDA accepts the above explanation, but considers that the applicant should conduct the survey immediately to confirm the safety and efficacy of duloxetine in the treatment of pain associated with OA, and to provide information about the results properly to healthcare professionals.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and the dosage and administration as shown below, with the following conditions. Since this was an application for the approval of the product for a new indication, the appropriate re-examination period should be 4 years.

Indications

○ Major depressive disorder

○ Pain associated with the following diseases:

Diabetic neuropathy

Fibromyalgia

Chronic low back pain[29]

<u>Osteoarthritis</u>

(Underline denote additions)

Dosage and Administration

1. Major depressive disorder

   Pain associated with diabetic neuropathy

   The usual adult dosage is 40 mg of duloxetine administered orally once daily after breakfast. The starting dose is 20 mg/day. The dose should be escalated by 20 mg/day at intervals of at least 1 week.

   The daily dose may be increased to up to 60 mg in patients with inadequate response to the dose of 40g/day.

2. Pain associated with fibromyalgia

29 After the submission of this application, the product was approved for the indication "pain associated with chronic low back pain" on March 18, 2016.

Pain associated with chronic low back pain

Pain associated with osteoarthritis

The usual adult dosage is 60 mg of duloxetine administered orally once daily after breakfast. The starting dose is 20 mg/day. The dose should be escalated by 20 mg/day at intervals of at least 1 week.

(Underline denote additions)

Condition of Approval The applicant is required to develop and appropriately implement a risk management plan.