Report on the Deliberation Results

September 4, 2015

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

[Brand name]	Loqoa Tape
[Non-proprietary name]	Esflurbiprofen (JAN*)/Mentha Oil
[Applicant]	Taisho Pharmaceutical Co., Ltd.
[Date of application]	October 20, 2014

[Results of deliberation]
In its meeting held on August 31, 2015, the Second Committee on New Drugs concluded that 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 8 years. The drug substance (esflurbiprofen) is classified as a poisonous drug and the drug product is classified as a powerful drug. Neither the drug substance nor the drug product is classified as a biological product or a specified biological product.

[Conditions of approval]
The applicant is required to develop and appropriately implement a risk management plan.

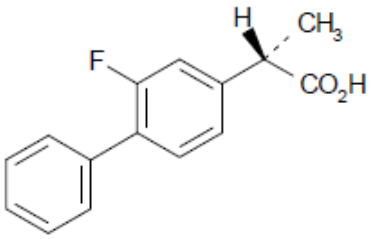
**Japanese Accepted Name (modified INN)*

Review Report

August 18, 2015
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.

[Brand name]	Loqoa Tape
[Non-proprietary name]	Esflurbiprofen/Mentha Oil
[Applicant]	Taisho Pharmaceutical Co., Ltd.
[Date of application]	October 20, 2014
[Dosage form/Strength]	Each plaster (10 cm × 14 cm) contains 40 mg of Esflurbiprofen and 36.2 mg of Mentha Oil.
[Application classification]	Prescription drug, (1) Drug with a new active ingredient, (2) New combination drug
[Chemical structure]	Esflurbiprofen



Molecular formula: $C_{15}H_{13}FO_2$
Molecular weight: 244.26
Chemical name:
(2*S*)-2-(2-Fluorobiphenyl-4-yl)propanoic acid

[Reviewing office]	Office of New Drug IV

Review Results

August 18, 2015

[Brand name]	Loqoa Tape
[Non-proprietary name]	Esflurbiprofen/Mentha Oil
[Applicant]	Taisho Pharmaceutical Co., Ltd.
[Date of application]	October 20, 2014

[Results of review]
On the basis of the data submitted, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the product has efficacy in the treatment of osteoarthritis, and that the product has acceptable safety in view of its benefits. The systemic exposure following application of 2 plasters of the product is comparable to the systemic exposure following administration of the approved products of oral flurbiprofen or intravenous flurbiprofen axetil. Therefore, the applicant should issue precautionary statements similar to those for these drugs. The applicant should also strongly advise healthcare professionals and patients not to apply more than 2 plasters at a time and to comply with the proper concomitant use of NSAIDs. In addition, post-marketing surveillance should be conducted to assess the occurrence of skin disorder, gastrointestinal disorder, renal dysfunction, and cardiovascular disorder and to evaluate the safety in elderly patients and in long-term use.

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

[Indication]
Relief of pain and inflammation associated with osteoarthritis

[Dosage and administration]
Apply Loqoa Tape to affected area once daily. Do not apply more than 2 plasters simultaneously.

[Conditions of approval]
The applicant is required to develop and appropriately implement a risk management plan.

Review Report (1)

July 24, 2015

I. Product Submitted for Approval

[Brand name]	Loqoa Tape
[Non-proprietary name]	Esflurbiprofen/Mentha Oil
[Applicant]	Taisho Pharmaceutical Co., Ltd.
[Date of application]	October 20, 2014
[Dosage form/Strength]	Each plaster (10 cm × 14 cm) contains 40 mg of Esflurbiprofen and 36.2 mg of Mentha Oil.
[Proposed indication]	Relief of pain and inflammation in symptoms indicated below: osteoarthritis.
[Proposed dosage and administration]	Apply Loqoa Tape to affected area once daily. Do not apply more than 2 plasters per day.

II. Summary of the Submitted Data and Outline of the Review by Pharmaceuticals and Medical Devices Agency

A summary of the submitted data and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery, use in foreign countries, and other information

[redacted]. In Japan, flurbiprofen (FP) was initially approved in August 1978 as a tablet formulation (Froben Tablets 40), and since then, granules and patches have been approved for the indication of relief of pain and inflammation associated with conditions including osteoarthritis. Also, an injectable solution containing flurbiprofen axetil as the active ingredient (Ropion Intravenous 50 mg) was approved in March 1992 for the indication of relief of postoperative and cancer-related pain.

[redacted]. However, mentha oil contained in Loqoa Tape was classified as an active ingredient for the following reasons: (a) There are prescription and over-the-counter (OTC) drugs containing mentha oil (as an active ingredient) at a concentration similar to that in Loqoa Tape; these drugs have been approved and used for many years for the treatment of arthralgia, etc. (b) "Points to consider in approval applications for drugs" (PFSB/ELD Notification No. 1121-12 dated November 21, 2014) states that, as a general rule, an excipient should be regarded as an active ingredient if its content is close to a therapeutic dose.

Osteoarthritis (OA) is characterized by symptoms such as pain, swelling, deformation, and limited range of motion in the joints of the limbs (e.g., the knee and hip joints), finger joints, spine, etc. The symptoms are caused by degenerative changes in articular cartilage and other articular components. In clinical practice in Japan, non-steroidal anti-inflammatory drugs (NSAIDs) are mainly used for alleviation of symptoms related to OA. According to the "Osteoarthritis Research Society International (OARSI) recommendations for the management of hip and knee osteoarthritis: OARSI evidence-based, expert consensus guidelines (adapted for Japanese patients by the Japanese Orthopaedic Association [JOA] Committee on Clinical Practice Guidelines on the Management of OA of the Knee)" (JOA Committee on Clinical Practice Guidelines on the Management of OA of the Knee, April 2015), oral NSAID therapy is most strongly recommended and topical NSAIDs are positioned as add-on or alternative to oral agents. Since topical NSAIDs still have room for improvement in efficacy, Loqoa Tape has been developed as

a new topical NSAID patch with improved dermal absorption and improved delivery to the target tissues, to ensure that Loqoa Tape is more effective than the conventional NSAID plaster. Data obtained during the development suggested that the systemic exposure following application of 2 plasters of 40 mg esflurbiprofen was comparable to the systemic exposure following administration of an approved oral FP. This suggested that esflurbiprofen plaster may pose a safety risk similar to that posed by the approved oral FP agents. The applicant considered that patients treated with a patch formulation are likely to use several patches simultaneously, possibly causing overdose. Therefore, the development of Loqoa Tape was focused only on OA, because patients with OA go through physician's check-up periodically, allowing physicians to check whether their patients are using Loqoa Tape properly. In Japan, the applicant initiated clinical development of Loqoa Tape in [redacted]. Based on the results from Japanese clinical studies etc., the applicant has filed a marketing approval application. As of July 2015, Loqoa Tape is not being developed outside Japan.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

[redacted].

[redacted].

2.A.(1).1) Characterization

Esflurbiprofen, one of the drug substances, is a white powder. The determined general properties include description, solubility, hygroscopicity, melting point, pH, optical rotation, dissociation constant, distribution coefficient, and crystalline polymorphism.

The chemical structure of the drug substance (esflurbiprofen) has been elucidated by elemental analysis, ultraviolet-visible spectroscopy (UV), infrared spectroscopy (IR), nuclear magnetic resonance spectroscopy (^{1}H-NMR, ^{13}C-NMR), mass spectrometry (MS), and single crystal X-ray crystallography. The drug substance (esflurbiprofen) contains one asymmetric carbon and is synthesized as an *S*-form.

2.A.(1).2) Manufacturing process

[redacted].

2.A.(1).3) Control of drug substance

The proposed specification for the drug substance (esflurbiprofen) include content, description, identification (IR), melting point, purity (heavy metals, related substances [high performance liquid chromatography (HPLC)], residual solvents [gas chromatography (GC)]), loss on drying, residue on ignition, and assay (HPLC).

2.A.(1).4) Stability of drug substance

Stability studies for the drug substance (esflurbiprofen) are shown in Table 1. The photostability test showed that the drug substance (esflurbiprofen) was photostable.

Table 1. Stability studies of drug substance

Study	Primary batch	Temperature	Humidity	Storage condition	Storage period
Long-term	3 pilot-scale batches	25°C	60%RH	Double-layered polyethylene bag	60 months
Accelerated	3 pilot-scale batches	40°C	75%RH		6 months

Based on the above, a retest period of 60 months has been proposed for the drug substance (esflurbiprofen) when stored at room temperature in a double-layered polyethylene bag.

2.A.(2) Drug product

2.A.(2).1) Description and composition of the drug product and formulation development

The drug product is a plaster formulation (10 cm × 14 cm) containing the drug substances: 40 mg of esflurbiprofen and 36.2 mg of mentha oil. It is comprised of an adhesive plaster base (1.73 g per plaster) containing the active ingredients, a backing layer, and a liner. [redacted].

[redacted].

2.A.(2).2) Manufacturing process

[redacted].

2.A.(2).3) Control of drug product

The proposed specification for the drug product include content, description, identification (HPLC/UV, thin-layer chromatography [TLC]), purity (related substances [HPLC]), shape (size measurement), mass, adhesion (ball tack test), release characteristics (HPLC), and assay (HPLC, GC).

2.A.(2).4) Stability of drug product

Stability studies for the drug product are shown in Table 2. The photostability test showed that the drug product was photolabile.

Table 2. Stability studies of drug product

Study	Primary batch	Temperature	Humidity	Storage configuration	Storage period
Long-term	3 production scale batches	25°C	60%RH	Laminated aluminum bag (containing 7 plasters)	24 months
Accelerated	3 production scale batches	40°C	75%RH		6 months

Based on the above, a shelf life of 24 months has been proposed for the drug product when stored at room temperature in a laminated aluminum bag. Long-term testing will be continued for [redacted] months.

2.B Outline of the review by PMDA

Based on the submitted data, PMDA has concluded that the quality of the drug substance and the drug product is controlled in an appropriate manner.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

The applicant investigated the *in vitro* inhibitory effect of esflurbiprofen on recombinant human cyclooxygenase (COX) (a primary pharmacodynamic study) and the *in vivo* effect on animal models of gonarthritis and footpad inflammation. The applicant also investigated the effects on the central nervous

system, cardiovascular system, and respiratory system (safety pharmacology studies). The applicant submitted data from a drug-drug interaction study with quinolone antibiotics (a pharmacodynamic drug interaction study). No secondary pharmacology studies were conducted to investigate esflurbiprofen's other effects than the COX inhibitory effects. This was because, according to the literature on esflurbiprofen or FP (the racemate of esflurbiprofen), esflurbiprofen's other effects are much weaker than the COX inhibitory effects, the mechanism of action of esflurbiprofen.

The applicant did not conduct any new pharmacology study on the pharmacological action or efficacy of mentha oil, because there were approved prescription and OTC drugs containing mentha oil (as an active ingredient) at a concentration similar to that in Loqoa Tape, and they had been used for many years to treat conditions including arthralgia.

Patches were used for dermal application unless otherwise specified. In a single study (except for some studies), the size of application area of each test substance was identical so that study results would not be affected by the difference in the size of application area.

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) COX inhibition

(a) Inhibition of recombinant human COX (4.2.1.1-11)

The inhibitory effect of esflurbiprofen against recombinant human COX-1 and COX-2 was investigated by measuring prostaglandin (PG) E_2 generation from arachidonic acid. Esflurbiprofen inhibited COX-1 and COX-2 in a concentration-dependent manner, with 50% inhibition (IC_{50}) of 8.97 and 2.94 nmol/L, respectively. IC_{50} of other test compounds against COX-1 and COX-2 was as follows: 29.5 and 4.96 μmol/L, respectively, for (*R*)-FP, 17.5 and 4.59 nmol/L, respectively, for FP, 33.4 and 48.9 nmol/L, respectively, for indomethacin, 38.2 and 26.1 nmol/L, respectively, for ketoprofen, and 1.47 μmol/L and 25.9 nmol/L, respectively, for the active metabolite of loxoprofen. IC_{50} of M1, the major metabolite of esflurbiprofen in human plasma, against COX-1 and COX-2 was 17.7 and 10.1 μmol/L, respectively.

(b) Inhibition of PGE_2 production in rat peritoneal cells (4.2.1.1-12)

The inhibitory effect of esflurbiprofen against PGE_2 production was investigated by measuring PGE_2 production in peritoneal cells of rats. IC_{50} of esflurbiprofen was 14 nmol/L. IC_{50} of (*R*)-FP, FP, indomethacin, and ketoprofen against PGE_2 production was 17, 0.052, 0.14, and 1.2 μmol/L, respectively.

3.(i).A.(1).2) Antinociceptive action (4.2.1.1-01 to 4.2.1.1-05)

(a) Effect against acute pain (4.2.1.1-01 to 4.2.1.1-02)

The effect of esflurbiprofen against acute pain was investigated in animal models of gonarthritis generated by administering 2% urate suspension (0.5 mL) into the knee joint cavity of male beagle dogs (n = 6/group). Immediately after injection of urate suspension, 0 (vehicle), 10, or 20 mg esflurbiprofen plaster, 40 mg FP patch, or 20 mg ketoprofen plaster was applied dermally. Compared with vehicle, esflurbiprofen 20 mg suppressed the increase in abnormal gait score[1] at 8 hours after the dermal application.

The effect of esflurbiprofen against acute pain was investigated in animal models of footpad inflammation generated by subcutaneous administration of 1% carrageenan saline solution (0.1 mL) to the right hind limb of male rats (n = 10/group). Then, 0 (vehicle), 1.5, or 3 mg esflurbiprofen plaster, 3 mg FP patch, or 3 mg ketoprofen plaster was applied dermally for 3 hours, and then the carrageenan saline solution was administered subcutaneously. At 3, 4, and 5 hours after the administration, the threshold of escape response to pressure stimulation to the inflamed leg was evaluated. The threshold increased at all measuring time points in all treatment groups except for the vehicle group.

(b) Effect against subacute pain (4.2.1.1-03 to 4.2.1.1-04)

The effect of esflurbiprofen against subacute pain was investigated in animal models of arthritis generated by administering 1% aqueous solution of silver nitrate (0.2 mL) to the hind limb joint of male rats (n = 10/group). At 22 hours after dosing of silver nitrate solution, the rats received a 3-hour dermal

[1] Rated on a 5-point scale from normal (0) to tripod gait (4).

application of a plaster containing 0 (vehicle), 0.33, 0.825, 1.65, or 3.3 mg of esflurbiprofen. The inflamed hind limb joint was stretched 5 times, and the frequency of phonation was counted every hour for 6 hours after the completion of the dermal application. The cumulative frequency of phonation per hour (from 1 to 6 hours after the completion of the dermal application) decreased in a dose-dependent manner.

Esflurbiprofen plaster 0 (vehicle), 1.65, or 3.3 mg, FP patch 3.3 mg, or ketoprofen plaster 3.3 mg was applied dermally for 3 hours to rat models of silver nitrate-induced arthritis generated in a similar manner as described above (n = 10/group). The frequency of phonation was counted every hour for 6 hours after the completion of the dermal application. The frequency of phonation decreased in all time periods in the esflurbiprofen 3.3 mg group compared with the vehicle group. The FP patch group did not show any decrease in the frequency of phonation in any time period. The ketoprofen plaster group showed a decrease in the frequency of phonation only at 3 hours after the completion of the dermal application.

(c) Effect against chronic pain (4.2.1.1-05)

The effect of esflurbiprofen against chronic pain was investigated in animal models of adjuvant arthritis generated by intracutaneous administration of 0.5% suspension of killed *Mycobacterium tuberculosis* in liquid paraffin (0.1 mL) into the tail base of male rats (n = 10/group). At 15 days after dosing of the suspension, the rats began to receive a dermal application of 0 (vehicle), 1.65, or 3.3 mg esflurbiprofen plaster, 3.3 mg FP patch, or 3.3 mg ketoprofen plaster, to the right hind limb, for 6 hours daily for 7 days. The threshold of escape response to pressure stimulation increased in the esflurbiprofen 3.3 mg group compared with the vehicle group. Compared with the FP and ketoprofen groups, the esflurbiprofen 3.3 mg group showed an increase in the cumulative threshold of escape response over the 7-day administration period.

3.(i).A.(1).3) Anti-inflammatory effect

(a) Effect against acute inflammation (4.2.1.1-06 to 4.2.1.1-08)

The effect of esflurbiprofen against acute inflammation was investigated in rat models of carrageenan-induced footpad inflammation generated by subcutaneous administration of 1% carrageenan saline solution (0.1 mL) to the right hind limb of male rats (n = 10/group). Esflurbiprofen plaster 0 (vehicle), 1.5, or 3 mg, FP patch 3 mg, or ketoprofen plaster 3 mg was applied dermally for 3 hours, and then 1% carrageenan saline solution was administered subcutaneously. The foot volume was measured at 3, 4, and 5 hours after the administration. Oedema was suppressed in the esflurbiprofen ≥1.5 mg groups, the FP patch group, and the ketoprofen plaster group, compared with the vehicle group.

The effect of esflurbiprofen against acute inflammation was investigated in animal models of contusion oedema in the right hind limb of male rats (n = 10/group). Rats received a 6-hour dermal application of esflurbiprofen plaster 0 (vehicle), 1.5, or 3 mg, FP patch 3 mg, or ketoprofen plaster 3 mg, and then received a contusion injury to the limb. The limb volume was measured at 2, 3, and 4 hours after the injury. Oedema was suppressed at all time points in the esflurbiprofen ≥1.5 mg and ketoprofen groups, compared with the vehicle group. In the FP patch group, oedema suppression was observed only at 2 hours after the injury.

Animal models of vascular hyperpermeability were generated by intracutaneous, subcutaneous, or intramuscular administration of 2% carrageenan saline solution (0.025 mL) to the right hind limb of male rats (n = 7/group). In the animal models, the effect of esflurbiprofen against vascular hyperpermeability was investigated by measuring the leakage of pigment following intravenous administration of 1% Evans blue saline solution. A plaster containing 3.3 mg esflurbiprofen or 3.3 mg ketoprofen was applied dermally for 2 hours, and then Evans blue saline solution was administered intravenously. The pigment was extracted from the limb tissue 1 hour later. Intracutaneous, subcutaneous, and intramuscular vascular hyperpermeability was suppressed in the esflurbiprofen group, compared with the untreated group. In the ketoprofen group, only intracutaneous vascular hyperpermeability was suppressed.

(b) Effect against chronic inflammation (4.2.1.1-09 to 4.2.1.1-10)

The effect of esflurbiprofen against chronic inflammation was investigated in animal models of adjuvant arthritis generated by intracutaneous administration of 0.5% suspension of killed *Mycobacterium*

tuberculosis in liquid paraffin (0.1 mL) into the tail base of male rats (n = 8/group). At 15 days after dosing of the suspension, the rats began to receive an esflurbiprofen plaster (0 [vehicle], 0.033, 0.0825, 0.33, 0.825, 1.65, or 3.3 mg), applied dermally to the right hind limb for 6 hours daily for 7 days. In the esflurbiprofen groups, swelling of the limb was suppressed in a dose-dependent manner. Compared with the vehicle group, the esflurbiprofen ≥0.33 mg groups showed suppression of the swelling from Day 3 of administration in the treated hind limb and from Day 2 in the untreated hind limb.

Rat models of adjuvant arthritis were generated in a similar manner as described above (n = 7/group). The rats received 0.5% suspension of killed *Mycobacterium tuberculosis* in liquid paraffin (0.1 mL). At 15 days after dosing, the rats began to receive a plaster containing 0 (vehicle), 0.05, 0.1, or 0.2 mg esflurbiprofen, or 0.05, 0.1, 0.2 mg ketoprofen, applied dermally to the right hind limb for 6 hours daily for 7 days. Swelling of the limb was suppressed in the esflurbiprofen ≥0.05 mg and ketoprofen 0.2 mg groups, compared with the vehicle group.

3.(i).A.(1).4) Comparison of dosing frequency (4.2.1.1-13)

The dosage regimen of esflurbiprofen for treating subacute pain was investigated in animal models of arthritis generated by administering 1% aqueous solution of silver nitrate (0.2 mL) to the right hind limb joint of male rats (n = 10/group). At 22 hours after dosing of silver nitrate solution, the rats began to receive a plaster containing 0 (vehicle) or 3.3 mg esflurbiprofen, applied dermally to the limb for 24 hours in total (vehicle, twice daily; esflurbiprofen, once or twice daily). The inflamed limb joint was stretched 5 times to count the frequency of phonation. The frequency of phonation decreased in both the esflurbiprofen twice- and once-daily groups, compared with the vehicle group, but the dosing frequency did not affect the frequency of phonation.

3.(i).A.(2) Safety pharmacology

Except for the study on hERG current, all safety pharmacology studies were conducted under non-GLP conditions before the enforcement of the "Safety Pharmacology Studies for Human Pharmaceuticals" (PMSB/ELD Notification No.902, June 21, 2001).

3.(i).A.(2).1) Effect on the central nervous system (4.2.1.3-01)

(a) Effect on clinical signs, behavior, activity, and anesthesia

Esflurbiprofen at 0 mg/kg (vehicle, 0.5% aqueous solution of carboxymethylcellulose sodium [0.5% CMC-Na solution]) or 0.1, 1, or 10 mg/kg was administered subcutaneously as a single dose to male mice (n = 3/group). The effect on the clinical signs and behavior was evaluated by Irwin's modified method. A slight increase in activity was observed in the 0.1 and 1 mg/kg groups. In the 10 mg/kg group, the activity of rats increased slightly and then decreased slightly. The 0.1 mg/kg group showed a slight increase in tactile response.

Esflurbiprofen (0 [vehicle, 0.5% CMC-Na solution], 0.1, 1, or 10 mg/kg) was administered subcutaneously as a single dose to male mice (n = 10/group), to evaluate the effect on activity and sleeping induced by hexobarbital sodium (80 mg/kg). Neither esflurbiprofen (at any dose) nor vehicle had effect on the activity or the induced sleep.

(b) Effect on convulsions

Esflurbiprofen (0 [vehicle, 0.5% CMC-Na solution], 0.1, 1, or 10 mg/kg) was administered subcutaneously as a single dose to male mice (n = 10/group). Esflurbiprofen (at any dose) had no effect on electroconvulsion or pentylenetetrazol-induced convulsions.

(c) Effect on nociceptive reaction

Esflurbiprofen (0 [vehicle, 0.5% CMC-Na solution], 0.1, 1, or 10 mg/kg) was administered subcutaneously as a single dose to male mice (n = 10/group), to investigate the effect on writhing behavior induced by chemical noxious stimulus caused by 0.6% acetic acid saline solution (10 mL/kg). Writhing frequency decreased by 64% and 84% in the 1 and 10 mg/kg groups, respectively, compared with that in the vehicle group.

Esflurbiprofen (0 [vehicle, 0.5% CMC-Na solution], 0.1, 1, or 10 mg/kg) was administered subcutaneously as a single dose to male mice (n = 10/group). The response to the noxious stimulus (pressure stimulus) caused by tail pinching was not affected in any groups.

(d) Effect on normal temperature

Esflurbiprofen (0 [vehicle, 0.5% CMC-Na solution], 0.1, 1, or 10 mg/kg) was administered subcutaneously as a single dose to male rats (n = 8/group). Rectal temperature was not affected in any groups.

3.(i).A.(2).2) Effect on the cardiovascular system

(a) Effect on hERG current (4.2.1.3-02)

Using human embryonic kidney cells (HEK 293 cells) expressing hERG potassium channel, the effect of esflurbiprofen on hERG current was investigated by the patch-clamp method. Esflurbiprofen at 0.1, 1, or 10 μmol/L did not affect hERG.

(b) Effect on blood pressure, heart rate, electrocardiogram, and blood flow (4.2.1.3-01)

Esflurbiprofen at 0 mg/kg (vehicle, 40% polyethylene glycol solution [40% PEG]) or 0.1, 1, or 10 mg/kg was administered intravenously as a single dose to male beagle dogs (n = 3/group). No effect was observed in blood pressure (systolic, diastolic, and mean), heart rate, or electrocardiogram (waveform, PR interval, QT interval, and QRS interval) in any groups.

3.(i).A.(2).3) Effect on the respiratory system (4.2.1.3-01)

Esflurbiprofen (0 [vehicle, 40% PEG], 0.1, 1, or 10 mg/kg) was administered intravenously as a single dose to male beagle dogs (n = 3/group). No effect was observed either in the respiratory rate or in the respiratory pressure.

3.(i).A.(2).4) Effect on the kidney and urinary system (4.2.1.3-01)

Esflurbiprofen (0 [vehicle, 0.5% CMC-Na solution], 0.1, 1, or 10 mg/kg) was administered subcutaneously as a single dose to male rats (n = 8/group), to investigate the effect on the kidney and urinary system. In the 1 and 10 mg/kg groups, chloride ion excretion in pooled urine (collected from 0 to 6 hours after dosing) decreased by 72% and 59%, respectively, and sodium/potassium ratio decreased by 65% and 59%, respectively. In the 10 mg/kg group, sodium ion excretion in pooled urine (collected from 0 to 6 hours after dosing) decreased by 67%. Urine volume between 6 and 24 hours after dosing increased by 194% and 217% in the 1 and 10 mg/kg groups, respectively. In the 1 mg/kg group, C_{max} of esflurbiprofen was 5.82 μg/mL and $AUC_{0\text{-}24h}$ was 48.5 μg·h/mL. These C_{max} and $AUC_{0\text{-}24h}$ values were 4.93 and 2.33 times, respectively, the values in humans treated with 40 mg esflurbiprofen (1 plaster of Loqoa Tape) (C_{max}, 1.18 μg/mL; $AUC_{0\text{-}24h}$, 20.80 μg·h/mL), and 2.15 and 1.03 times the values in humans treated with 80 mg esflurbiprofen (2 plasters of Loqoa Tape) (C_{max}, 2.71 μg/mL; $AUC_{0\text{-}24h}$, 47.00 μg·h/mL).

3.(i).A.(2).5) Effect on the gastrointestinal system (4.2.1.3-03 to 4.2.1.3-04)

(a) Gastric ulcer-inducing effect

A plaster containing 0 (vehicle), 1, 3, 10, or 30 mg/kg esflurbiprofen, or 3, 10, or 30 mg/kg ketoprofen was applied dermally to male rats (n = 10/group), and the gastric ulcer-inducing effect was investigated at 24 hours after dosing. Gastric ulcer was observed in the esflurbiprofen ≥3 mg/kg and ketoprofen 30 mg/kg groups. In the animals with gastric ulcer induced by esflurbiprofen or ketoprofen, the minimum C_{max} observed was 3.9 and 5.6 μg/mL, respectively, for esflurbiprofen and ketoprofen, and the minimum $AUC_{0\text{-}24h}$ was 35.8 and 64.1 μg·h/mL, respectively, for esflurbiprofen and ketoprofen.

Male rats (n = 10/group) received dermal esflurbiprofen plaster 0 (vehicle), 1, 3, 10, or 30 mg/kg, or oral suspension containing 0 (vehicle, 0.5% hydroxypropyl methylcellulose solution [0.5% HPMC]), 0.1, 0.3, 1, or 3 mg/kg esflurbiprofen. The gastric ulcer-inducing effect was investigated at 24 hours after dosing. Gastric ulcer was observed in animals given dermal esflurbiprofen ≥3 mg/kg and those given oral esflurbiprofen ≥0.1 mg/kg. In the animals with gastric ulcer, the minimum C_{max} of esflurbiprofen was 1.70μg/mL (dermal) and 0.25 μg/mL (oral), and the minimum $AUC_{0\text{-}24h}$ was 26.01 μg·h/mL (dermal) and 2.49 μg·h/mL (oral). Thus, C_{max} and $AUC_{0\text{-}24h}$ were approximately 7 and

10 times, respectively, higher in animals showing gastric ulcer after dermal application than in animals showing gastric ulcer after oral administration.

In animals with gastric ulcer induced by dermal esflurbiprofen, esflurbiprofen exposure was close to that in humans receiving esflurbiprofen 40 mg (C_{max}, 1.18 μg/mL; $AUC_{0\text{-}24h}$, 20.80 μg·h/mL) and lower than that in humans receiving esflurbiprofen 80 mg (C_{max}, 2.71 μg/mL; $AUC_{0\text{-}24h}$, 47.00 μg·h/mL).

(b) Effect on gastrointestinal transport (4.2.1.3-01)
Esflurbiprofen (0 [vehicle, 0.5% CMC-Na solution], 0.1, 1, or 10 mg/kg) was administered subcutaneously as a single dose to male mice (n = 10/group), and then charcoal powder suspension[2] (10 mL/kg) was administered orally. Gastrointestinal transport of charcoal powder was not affected in any groups.

3.(i).A.(2).6) Effect on the autonomic nervous system (4.2.1.3-01)
Esflurbiprofen (0 [vehicle, 1% dimethyl sulfoxide (DMSO)], 0.1, 1, or 10 μmol/L) had no effect on the spontaneous motility of the ileum isolated from male rabbits (n = 5/group).

In the ileum isolated from male guinea pigs (n = 5/group), esflurbiprofen (0 [vehicle, 1% DMSO], 0.1, 1, or 10 μmol/L) had no effect on the maximum contraction induced by constrictors (acetylcholine 0.1 μmol/L, histamine 1 μmol/L, serotonin 5 μmol/L, or barium chloride 1 mmol/L).

3.(i).A.(2).7) Other effects (4.2.1.3-01)
(a) Effect on platelet aggregation
Esflurbiprofen (0 [vehicle, 1% DMSO], 0.1, 1, or 10 μmol/L) was added to platelet-rich plasma isolated from the blood collected from male rabbits (n = 4/group), to investigate the effect on platelet aggregation induced by adenosine diphosphate (ADP) (3 μmol/L) or collagen (20 μg/mL). In the 10 μmol/L group, collagen-induced aggregation decreased by 34%, whereas ADP-induced aggregation was not affected. The minimum esflurbiprofen concentration that suppressed platelet aggregation (10 μmol/L) was 2.1 and 0.9 times, respectively, the C_{max} in humans receiving esflurbiprofen 40 mg (1.18μg/mL) and 80 mg (2.71 μg/mL).

(b) Effect on blood coagulation
Esflurbiprofen (0 [vehicle, 0.5% CMC-Na solution], 0.1, 1, or 10 mg/kg) was administered subcutaneously as a single dose to male rats (n = 5/group). No effect was observed on prothrombin time, activated partial thromboplastin time, or fibrinogen in the plasma separated from blood samples in any groups.

(c) Effect on fibrinolytic capacity
Esflurbiprofen (0 [vehicle, 1% DMSO], 0.1, 1, or 10 μmol/L) had no effect on the fibrinolytic capacity of plasma separated from blood samples obtained from male rabbits (n = 4/group).

(d) Effect on lipid metabolism
Esflurbiprofen (0 [vehicle, 0.5% CMC-Na solution], 0.1, 1, or 10 mg/kg) was administered subcutaneously as a single dose to male rats (n = 5/group). No effect was observed on the total cholesterol or triglycerides in the plasma in any groups.

3.(i).A.(3) Pharmacodynamic interactions
3.(i).A.(3).1) Drug interactions with quinolone antibiotics
(a) Effect on the binding to $GABA_A$ receptors (4.2.1.4-01 to 4.2.1.4-02)
Using crude synaptic membrane preparation obtained from the cerebral cortex of male rats (n = 3/group), the effect of esflurbiprofen, ketoprofen, indomethacin, and 4-biphenylacetic acid on the binding of ^{3}H-labeled muscimol to γ-aminobutyric acid $(GABA)_A$ receptors was investigated in the presence or absence of enoxacin (10 μmol/L). In the absence of enoxacin, esflurbiprofen, ketoprofen, and 4-biphenylacetic acid (maximum concentration, 1000 μmol/L) did not affect the binding of ^{3}H-labeled muscimol, whereas only indomethacin inhibited the binding of ^{3}H-labeled muscimol with an IC_{50} of

[2] Charcoal powder 5 g was suspended in 100 mL of 10% gum arabic solution.

640 μmol/L. In the presence of enoxacin, all test substances including esflurbiprofen inhibited the binding of ^{3}H-labeled muscimol with IC_{50} of 9.0 μmol/L for esflurbiprofen, 4.3 μmol/L for ketoprofen, 34 μmol/L for indomethacin, and 0.28 μmol/L for 4-biphenylacetic acid.

Using crude synaptic membrane preparation obtained from the cerebral cortex of male rats (n = 3/group), the effect of esflurbiprofen, (*R*)-FP, and 4-biphenylacetic acid on the binding of ^{3}H-labeled muscimol to $GABA_A$ receptors was investigated in the presence of enoxacin (10 μmol/L). IC_{50} was 7.6 μmol/L for esflurbiprofen, 0.74 μmol/L for (*R*)-FP, and 0.28 μmol/L for 4-biphenylacetic acid.

(b) Effect on GABA-induced Cl^- current (4.2.1.4-03)
Using dorsal root ganglion neurons obtained from male and female frogs (n = 5/group), the effect of esflurbiprofen, (*R*)-FP, and 4-biphenylacetic acid on GABA (10 μmol/L)-induced Cl^- current in the presence or absence of enoxacin (10 μmol/L) was investigated by the plaster-clamp method. In the absence of enoxacin, GABA-induced Cl^- current was inhibited by 7%, 12%, and 8%, respectively, by esflurbiprofen, (*R*)-FP, and 4-biphenylacetic acid at the maximum concentration of 100 μmol/L. In the presence of enoxacin, GABA-induced Cl^- current was inhibited by esflurbiprofen, (*R*)-FP, and 4-biphenylacetic acid in a concentration-dependent manner with IC_{50} of 10.9, 1.06, and 0.739 μmol/L, respectively.

(c) Convulsion-inducing effect (4.2.1.4-04 to 4.2.1.4-06)
Male mice (n = 8/group) were given oral esflurbiprofen (0 [vehicle, 0.5% HPMC], 0.1, 1, or 10 mg/kg) or oral fenbufen (100 mg/kg), followed by oral administration of enoxacin (100 mg/kg), levofloxacin (100 mg/kg), or ciprofloxacin (100 mg/kg), to investigate the convulsion-inducing effect of the drugs. Animals given fenbufen and enoxacin showed clonic convulsions and tonic convulsions and all died within 6 hours. Animals given esflurbiprofen and enoxacin had no convulsions regardless of esflurbiprofen dose. No convulsions were observed in animals given esflurbiprofen (10 mg/kg) in combination with levofloxacin or ciprofloxacin.

Male mice (n = 10/group) were given oral administration of esflurbiprofen (30-150 mg/kg), (*R*)-FP (10-100 mg/kg), or fenbufen (10-100 mg/kg), followed by oral administration of enoxacin (400 mg/kg), to investigate the convulsion-inducing effect of the drugs. Animals receiving ≥60 mg/kg esflurbiprofen, ≥30 mg/kg (*R*)-FP, or ≥10 mg/kg fenbufen showed convulsions or died.

Male mice (n = 10/group) received a dermal application of esflurbiprofen plaster (0 [vehicle], 100-300 mg/kg), (*R*)-FP patch (100-300 mg/kg), or FP patch (100-300 mg/kg), followed by oral administration of enoxacin (400 mg/kg), to investigate the convulsion-inducing effect of the drugs. Animals given esflurbiprofen and enoxacin had no convulsions regardless esflurbiprofen dose. Animals receiving ≥200 mg/kg of (*R*)-FP or FP showed convulsions.

The applicant's explanation about the results of the above safety pharmacology studies:
Esflurbiprofen exhibited peripheral antinociceptive actions, induced gastric ulcer, affected urine volume and urinary electrolytes, and inhibited platelet aggregation. All of these effects were probably due to COX inhibition, a pharmacological action of esflurbiprofen. Since COX inhibition is common to non-steroidal anti-inflammatory drugs (NSAIDs), the effects were not specific to esflurbiprofen.

3.(i).B Outline of the review by PMDA
PMDA concluded that the submitted data elucidate the pharmacological action of esflurbiprofen and that esflurbiprofen, the (*S*)-enantiomer of FP, is largely responsible for the pharmacological action of FP, a racemate. In safety pharmacology studies, esflurbiprofen induced gastric ulcer, affected urinary electrolytes, and inhibited platelet aggregation; these effects were observed at an exposure similar to that in humans receiving the clinical dose. Therefore, the risk of these effects in patients receiving esflurbiprofen in clinical settings should be carefully assessed based on the clinical study results [see "4.(iii).B.(2) Safety"].

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

The applicant submitted data on the absorption, distribution, metabolism, excretion, and drug interactions of esflurbiprofen (the results of studies on dermal and intravenous administration in rats and dogs). Pharmacokinetics were investigated using ^{14}C-labeled or unlabeled esflurbiprofen. Unchanged esflurbiprofen in each biological sample was measured by high performance liquid chromatography with fluorometric detector (HPLC-FL) (lower limit of quantitation, 0.01 or 0.025 μg/mL for rat plasma, 0.02 or 0.025 μg/mL for hairless rat plasma, 0.01 μg/mL for dog plasma, 5 μg/g for rat skin, and 0.025 μg/g for rat muscle). Radioactivity in each biological sample was measured by liquid scintillation counter (lower limit of quantitation, twice the background level).

In the pharmacokinetic studies presented below, patches were used for dermal application unless otherwise specified. Pharmacokinetic parameter are expressed as means (± standard deviation [SD]).

3.(ii).A.(1) Absorption

3.(ii).A.(1).1) Single-dose studies (4.2.2.2-01 to 4.2.2.2-05)

Table 3 shows the pharmacokinetic parameters of unchanged esflurbiprofen and the total radioactivity concentration in plasma following a 24-hour dermal application or a single intravenous administration of unlabeled or ^{14}C-labeled esflurbiprofen to male rats and male dogs. The absolute bioavailability of dermal application was 95.9% in hairless rats and 16.1% in dogs, compared with the intravenous administration.

Table 3. Pharmacokinetic parameters of esflurbiprofen following a single dose of unlabeled or ^{14}C-labeled esflurbiprofen to rats and dogs

Animal	Dose (mg/kg)	Number of animals	Route of administration	C_{max} (μg/mL)	T_{max} (h)	$AUC_{0-\infty}$ (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_{ss} (mL/kg)
Rats	0.3[a)]	4 males	d.a.	1.1 ± 0.1	9.0 ± 2.0	20.2 ± 1.9	7.3 ± 1.7	-	-
	1[a)]			3.1 ± 0.3	9.5 ± 3.0	64.4 ± 6.6	7.6 ± 0.9	-	-
	3[a)]			9.3 ± 1.8	7.5 ± 3.4	172.2 ± 18.1	6.7 ± 0.7	-	-
	1[a)]		d.a.[c)]	4.0 ± 0.6	3.5 ± 1.0	63.1 ± 15.1	6.8 ± 0.9	-	-
	1[a)]		i.v.	11.8 ± 0.8[d)]	-	85.8 ± 11.5	5.9 ± 0.8	11.5 ± 1.3	85.1 ± 2.4
Hairless rats	0.3[b)]	5 males	d.a.	1.0 ± 0.2	5.6 ± 1.7	14.8 ± 1.0	5.4 ± 0.7	-	-
	1[b)]			2.7 ± 0.5	6.4 ± 1.7	44.0 ± 6.7	6.6 ± 0.2	-	-
	3[b)]			8.2 ± 1.6	4.8 ± 1.8	118.5 ± 13.4	6.6 ± 0.4	-	-
	1	4 males	i.v.	12.0 ± 0.2[d)]	-	45.8 ± 2.1	4.1 ± 0.2	22 ± 1	118 ± 5
	1	4 males	d.a.	2.7 ± 0.3	6.0 ± 1.6	44.1 ± 2.9	6.2 ± 0.2	-	-
	2.5			6.0 ± 1.2	7.0 ± 1.2	99.0 ± 9.5	5.3 ± 0.5	-	-
	5	5 males		13.0 ± 2.2	7.2 ± 1.1	198.9 ± 16.8	5.7 ± 0.3	-	-
	10			25.7 ± 5.6	5.6 ± 1.7	382.0 ± 21.8	5.2 ± 0.4	-	-
Dogs	1[a)]	3 males	d.a.	0.6 ± 0.1	24.0 ± 0.0	59.7 ± 12.1	57.8 ± 2.7	-	-
	1[a)]		i.v.	13.9 ± 0.8[d)]	-	490.3 ± 60.9	37.1 ± 2.2	2.2 ± 0.3	105.5 ± 3.8
	0.3[b)]	4 males	d.a.	0.6 ± 0.3	24	66.7 ± 39.5	72.5 ± 6.0	-	-
	1[b)]			1.0 ± 0.4	24	126.9 ± 46.5	78.2 ± 15.0	-	-
	1		i.v.	17.8 ± 1.9[d)]	-	787.7 ± 196.2	48.1 ± 3.1	1.4 ± 0.4	87 ± 19

Mean or mean ± SD;

Abbreviations: -, no data available; C_{max}, maximum concentration; T_{max}, time to maximum concentration; AUC, area under the concentration-time curve; $t_{1/2}$, elimination half-life; CL, total body clearance; V_{ss}, distribution volume under a steady state; d.a., dermal application; i.v., intravenous administration

a) ^{14}C-labeled esflurbiprofen was administered;

b) Dose was adjusted by the application area;

c) Application to skin damaged by abrasion of keratinous layer;

d) Concentration at 5 minutes after administration

3.(ii).A.(1).2) Repeated-dose studies (toxicokinetics) (4.2.3.2-04 to 4.2.3.2-06, 4.2.3.2-08, 4.2.3.2-09)

Toxicokinetics of esflurbiprofen was investigated in repeated dermal application studies in rats (13 weeks and 6 months) and dogs (13 weeks and 12 months). Table 4 shows the pharmacokinetic parameters following repeated administration. Esflurbiprofen accumulated with repeated administration, and esflurbiprofen exposure tended to be higher in female rats than in male rats.

Table 4. Pharmacokinetic parameters of esflurbiprofen following repeated doses of esflurbiprofen to rats and dogs

	Duration of treatment	Dose (mg/kg)	Number of animals	Route of administration	Time point	Male		Female	
						C_{max} (μg/mL)	AUC_{0-24h} (μg·h/mL)	C_{max} (μg/mL)	AUC_{0-24h} (μg·h/mL)
Rats	13 weeks	0.03	4 males 4 females	d.a.	Day 1	0.0038[a)]	0.050[a)]	0.021[b)]	0.37[b)]
					Week 13	0.044	0.88	0.11	2.06
		0.1			Day 1	0.045	0.71	0.048	0.83
					Week 13	0.19	3.28	0.36	4.67
		0.3			Day 1	0.21	3.52	0.14	2.31
					Week 13	0.44	8.65	0.84	14.7
	13 weeks	1	4 males 4 females	d.a.	Day 1	0.13[b)]	1.88[b)]	0.24	3.76
					Week 13	1.69	28.5	1.59	28.8
		3			Day 1	0.45	7.06	2.88	41.1
					Week 13	4.62	72.1	6.62	106.8
		10			Day 1	2.61	36.8	1.89	33.1
					Week 13	13.6[c)]	224.3[c)]	9.00	168.6
	26 weeks	0.1	4 males 4 females	d.a.	Day 1	0.014[d)]	0.18[d)]	0.071[b)]	0.88[b)]
					Week 26	0.090	1.80	0.14	2.83
		0.3			Day 1	0.074	0.58	0.21	3.66
					Week 26	0.31	6.29	0.59	11.7
		1			Day 1	0.088	1.41	0.22	3.47
					Week 26	0.45	8.63	1.72	33.8
Dogs	13 weeks	0.1	5 males 5 females	d.a.	Day 1	ND[c)]	NC[c)]	ND[c)]	NC[c)]
					Week 13	0.047[c)]	0.91[c)]	0.087[c)]	1.81[c)]
		0.3			Day 1	0.099[e)]	1.05[e)]	0.010[f)]	0.079[f)]
					Week 13	0.80	16.4	0.45	9.28
		1			Day 1	0.60	6.04	0.65	7.55
					Week 13	1.22	24.5	2.06	40.3
	52 weeks	0.03	4 males 4 females	d.a.	Day 1	0.063	0.44	0.020	0.16
					Week 52	0.16	3.35	0.15	3.23
		0.1			Day 1	0.064	0.51	0.069	0.62
					Week 52	0.46	8.93	0.35	7.49
		0.3			Day 1	0.081	0.77	0.14	1.27
					Week 52	0.82	16.1	0.83	16.4

Mean;
Abbreviations: d.a., dermal application; C_{max}, maximum concentration; AUC, area under the concentration-time curve; ND, not detectable (<0.01 μg/mL); NC, not calculated;
a) Below the lower limit of quantitation (<0.01 μg/mL) in 3 of 4 animals;
b) Below the lower limit of quantitation (<0.01 μg/mL) in 1 of 4 animals;
c) n = 3;
d) Below the lower limit of quantitation (<0.01 μg/mL) in 2 of 4 animals;
e) Below the lower limit of quantitation (<0.01 μg/mL) in 2 of 5 animals;
f) Below the lower limit of quantitation (<0.01 μg/mL) in 1 of 5 animals.

3.(ii).A.(2) Distribution

3.(ii).A.(2).1) Tissue distribution (4.2.2.2-01, 4.2.2.3-01)

^{14}C-labeled esflurbiprofen (1 mg/kg) was applied dermally for 24 hours as a single dose to male albino rats (n = 4/time point). Radioactivity was distributed throughout the whole body. Tissue radioactivity concentrations were lower than plasma radioactivity concentrations, except for concentrations in the skin at the application site and in the cutaneous muscle beneath the application site. Radioactivity concentrations peaked at 2 hours after the beginning of treatment in the skin at the application site and in the cutaneous muscle beneath the application site, at 24 hours in the cecum and colon, and at 8 hours in other tissues. In the skin at the application site, the radioactivity concentration at 72 hours was 17% of the maximum concentration. In other tissues, the radioactivity concentration at 72 hours was <10% of the maximum concentration or below the detection limit.

A single dose of ^{14}C-labeled esflurbiprofen (1 mg/kg) was administered subcutaneously to male pigmented rats (n = 3/time point). At 1 and 24 hours postdose, the radioactivity concentration in the pigmented skin was comparable to that in the non-pigmented skin, and both pigmented and albino rats had a similar ratio of “the radioactivity concentration in the eyeball” to plasma radioactivity concentration. These results suggested that esflurbiprofen is unlikely to be specifically distributed in melanin-containing tissues.

3.(ii).A.(2).2) Distribution in subcutaneous tissues in animal models of inflammation (4.2.2.3-02)

Esflurbiprofen (4.8 mg/kg) was applied dermally to animal models of inflammation generated by administering 1% carrageenan to the hind footpad of male rats (n = 5/group), to measure esflurbiprofen concentration in plasma, the skin at the application site, and the muscle beneath the application site. At 6 hours after the beginning of treatment, plasma esflurbiprofen concentration was 5.59 ± 0.78 μg/mL. Tissue esflurbiprofen concentrations were 487 ± 101 μg/g in the skin, 3.83 ± 2.30 μg/g in the foot muscle at the application site, and 0.73 ± 0.13 μg/g in the foot muscle at the non-application site.

3.(ii).A.(2).3) Plasma protein binding and distribution in blood cells (4.2.2.2-01, 4.2.2.2-02, 4.2.2.3-04)

The *in vitro* plasma protein binding of ^{14}C-labeled esflurbiprofen at 10 μg/mL was 99.91% in rats, 99.94% in dogs, and 99.95% in humans. The fraction of ^{14}C-labeled esflurbiprofen (1 μg/mL) bound to human serum albumin, human γ-globulin, and α_1-acid glycoprotein was estimated to be >99.74%, 18.7%, and 32.9%, respectively.

The *in vitro* distribution of ^{14}C-labeled esflurbiprofen (0.1, 1, and 10 μg/mL) in blood cells was 7.3% to 9.2% in rats, 2.8% to 7.9% in dogs, and 3.9% to 6.0% in humans, showing no correlation between the ^{14}C-labeled esflurbiprofen concentration and the binding rate to blood cells.

Following a 24-hour dermal application of ^{14}C-labeled esflurbiprofen (1 mg/kg) to male rats, the plasma protein binding at 2, 8, 24, and 48 hours after the beginning of treatment was 99.5% to 99.9%.

Following a 24-hour dermal application of ^{14}C-labeled esflurbiprofen (1 mg/kg) to male dogs, the plasma protein binding at 8, 24, 48, and 120 hours after the beginning of treatment was 99.5% to 100.0%.

3.(ii).A.(2).4) Placental transfer (4.2.2.3-05)

A single dose of ^{14}C-labeled esflurbiprofen (1 mg/kg) was administered subcutaneously to female rats at Gestation Day 18 (n = 3/time point). Radioactivity concentration at 1, 8, and 24 hours postdose was 5.3 ± 0.3, 3.1 ± 0.2, and 0.6 ± 0.2 μg eq./mL, respectively, in maternal blood and 0.8 ± 0.1, 0.7 ± 0.1, and 0.2 ± 0.1 μg eq./mL, respectively, in fetal blood.

3.(ii).A.(3) Metabolism

3.(ii).A.(3).1) *In vivo* studies (4.2.2.4-01, 4.2.2.4-0.2, 5.3.3.1-03)

Male rats (n = 4/group) received a 24-hour dermal application of ^{14}C-labeled esflurbiprofen (1 mg/kg). Unchanged esflurbiprofen and M1 (4'-hydroxylated form of esflurbiprofen) were detected in plasma. The proportion of unchanged esflurbiprofen and M1 in plasma (expressed as a percentage of the total radioactivity) was 88.3% and 5.9%, respectively, at 8 hours after the beginning of treatment, and 75.8% and 15.5%, respectively, at 24 hours. Up to 96 hours after the beginning of treatment, M1, M2 (3'-hydroxylated form of M1), and M3 (methyl conjugate of M2) were detected in urine, and unchanged esflurbiprofen, M1, and M2 were detected in feces. Biliary cannulated rats received a for 24-hour dermal application of ^{14}C-labeled esflurbiprofen (1 mg/kg). Unchanged esflurbiprofen and M1 were detected in the bile up to 48 hours after the beginning of treatment. A study using β-glucuronidase/arylsulfatase and saccharic acid 1,4-lactone (inhibitor of β-glucuronidase) suggested that, in urine and bile, unchanged esflurbiprofen and M3 were present as glucuronide conjugates, M1 as glucuronide conjugates, and M2 as sulfate conjugates. In the skin at the application site, the main radioactivity detected was unchanged esflurbiprofen, accounting for 88.4% and 81.9% of the total radioactivity, respectively, at 8 and 24 hours after the beginning of treatment.

Male dogs (n = 3/group) received a 24-hour dermal application of ^{14}C-labeled esflurbiprofen (1 mg/kg). In plasma, only unchanged esflurbiprofen was detected, accounting for 46.3% and 20.6% of the total radioactivity, respectively, at 24 and 72 hours after the beginning of treatment. M4 (taurine conjugate of esflurbiprofen) was detected in urine up to 168 hours after the beginning of treatment, and unchanged esflurbiprofen, M1, M3, and M4 in feces up to 168 hours.

Seven healthy adult men received a 24-hour dermal application of SFPP-1 (an esflurbiprofen 20 mg formulation developed for clinical studies). Unchanged esflurbiprofen, glucuronide conjugate of

unchanged esflurbiprofen, and M1 were detected in plasma of the subjects. The ratio of $AUC_{0\text{-}71h}$ (the glucuronide conjugate of unchanged esflurbiprofen/unchanged esflurbiprofen) was approximately 5%. At 10 hours after the beginning of treatment, the ratio of plasma M1 concentration to plasma esflurbiprofen concentration was approximately 4%. The following species were detected in urine up to 72 hours after the beginning of treatment: unchanged esflurbiprofen (accounting for 0.3% of the administered dose), glucuronide conjugate of unchanged esflurbiprofen (10.4%), M1 (1.0%), glucuronide conjugate of M1 (9.0%), sulfate conjugate of M1 (9.0%), and glucuronide conjugate of M3 (4.2%).

Figure 1 shows the metabolic pathways of esflurbiprofen, suggested by the results of the above metabolic studies.

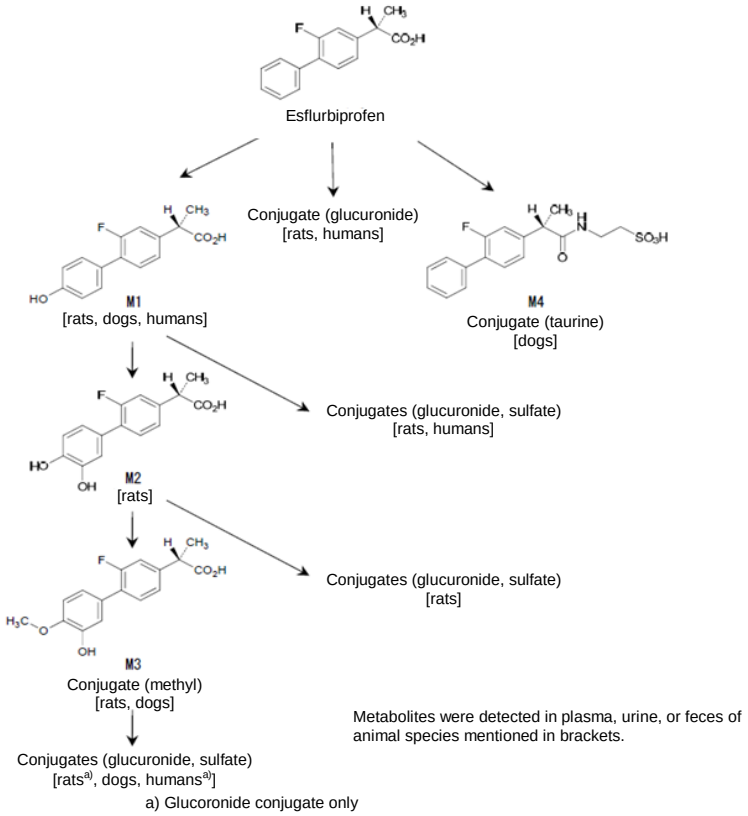


Figure 1. Postulated metabolic pathways of esflurbiprofen

3.(ii).A.(3).2) *In vivo* chiral inversion of the optical isomer of esflurbiprofen (4.2.2.2-06, 4.2.2.4-03, 5.3.3.1-03)

Following a dermal application of esflurbiprofen (10 mg/kg) to male rats (n = 5), (*R*)-FP was not detected in plasma up to 48 hours after the beginning of treatment (<0.025 μg/mL).

Following an oral administration of esflurbiprofen (30 mg/kg) to male mice (n = 5/group), $AUC_{0\text{-}10h}$ of esflurbiprofen and (*R*)-FP was 419.8 and 30.7 μg·h/mL, respectively. Following a single oral administration of (*R*)-FP (30 mg/kg), $AUC_{0\text{-}10h}$ of esflurbiprofen and (*R*)-FP was 294.3 and 574.8 μg·h/mL, respectively.

Following a single dermal application of esflurbiprofen (20 mg) to 7 healthy adult men, the plasma concentration of esflurbiprofen and (*R*)-FP at 10 hours after the beginning of treatment was 413.4 ± 122.5 and 2.5 ± 1.4 ng/mL, respectively.

3.(ii).A.(3).3) Cytochrome P450 enzymes involved in the metabolism of esflurbiprofen (4.2.2.4-04)

The following study was conducted because CYP2C9, an isozyme of cytochrome P450 (CYP), is involved in the metabolism of esflurbiprofen (Tracy TS et al. *Biochem Pharmacol*. 1996;52:1305-1309).

Esflurbiprofen (0.5-100 μmol/L) was added to human liver microsomes prepared from subjects with different CYP2C9 genotypes (*CYP2C9 *1/*1*, extensive metabolizer [EM] or *CYP2C9 *3/*3*, poor metabolizer [PM]). CL_{int} of esflurbiprofen was 180 μL/min/mg protein in the liver microsomes with genotype *CYP2C9 *1/*1* and 2.6 μL/min/mg protein in the liver microsomes with genotype *CYP2C9 *3/*3*, with the PM/EM ratio for CL_{int} being approximately 1/69.

3.(ii).A.(4) Excretion

3.(ii).A.(4).1) Fecal and biliary excretion (4.2.2.2-01, 4.2.2.2-02)

Male rats (n = 4/group) received a 24-hour dermal application of ^{14}C-labeled esflurbiprofen (0.3, 1, and 3 mg/kg) or a single intravenous administration of ^{14}C-labeled esflurbiprofen 1 mg/kg. The urinary excretion rate of radioactivity up to 168 hours after the beginning of treatment was 37.1% (dermal 0.3 mg/kg), 43.5% (dermal 1 mg/kg), 43.3% (dermal 3 mg/kg), and 52.3% (intravenous). The fecal excretion rate of radioactivity was 31.0% (dermal 0.3 mg/kg), 40.3% (dermal 1 mg/kg), 43.5% (dermal 3 mg/kg), and 44.2% (intravenous). After the 24 hour-dermal application of ^{14}C-labeled esflurbiprofen 0.3, 1, and 3 mg/kg, 30.2%, 16.9%, and 14.4%, respectively, of radioactivity remained in the plaster. The radioactivity excretion rate following dermal application to the skin damaged by abrasion of the keratinous layer, was comparable to that following administration to intact skin.

Biliary cannulated male rats (n = 4) received a 24-hour dermal application of ^{14}C-labeled esflurbiprofen (1 mg/kg). The biliary excretion rate of radioactivity at 48 hours after the beginning of treatment was 57.7%. The radioactivity excreted into bile was then administered into the duodenum. At 48 hours after the dose into the duodenum, the excretion rate of radioactivity was 20.7% in urine, 6.5% in feces, and 70.2% in bile.

Male dogs (n = 3/group) received a 24-hour dermal application or a single intravenous administration of ^{14}C-labeled esflurbiprofen (1 mg/kg). At 336 hours after the beginning of treatment, urinary excretion rate of radioactivity was 4.9% (dermal) and 57.4% (intravenous) and the fecal excretion rate was 4.5% (dermal) and 37.8% (intravenous). After the 24-hour dermal application of ^{14}C-labeled esflurbiprofen 1 mg/kg, 85.9% of radioactivity remained in the plaster.

3.(ii).A.(4).2) Excretion in milk (4.2.2.3-05)

Lactating rats (n = 3/time point) received a single subcutaneous administration of ^{14}C-labeled esflurbiprofen (1 mg/kg). At 1 hour postdose, radioactivity concentration in plasma and milk of maternal animals was 7.9 ± 0.8 and 0.7 ± 0.1 μg eq./mL, respectively. At 24 hours postdose, $AUC_{0\text{-}24h}$ in plasma and milk was 65.9 ± 6.0 and 11.1 ± 2.3 μg eq.·h/mL, respectively.

3.(ii).A.(5) Pharmacokinetic drug interactions

3.(ii).A.(5).1) Enzyme inhibition (4.2.2.6-01)

The inhibitory effect of esflurbiprofen (0.8, 4, 20, 100, or 500 μmol/L) against human CYP isozymes was investigated using human liver microsomes. IC_{50} was 90.7 μmol/L for CYP2C9, 142 μmol/L for CYP2B6, 373 μmol/L for CYP2C8, and 373 μmol/L for CYP2C19. IC_{50} for CYP1A2, CYP2A6, CYP2D6, CYP2E1, and CYP3A4 was estimated to be higher than the maximum concentration tested (500 μmol/L). IC_{50} for CYP2C9 was approximately 14 to 34 times the C_{max} (654.3-1605.8 ng/mL, 2.68-6.57 μmol/L) in healthy adult men receiving dermal application of 2 plasters of 20 mg esflurbiprofen (SFPP-2). Based on the above, the applicant explained that drug interactions due to CYP inhibition are unlikely to occur in clinical use.

3.(ii).B Outline of the review by PMDA

PMDA's view:

The *in vivo* behavior of esflurbiprofen has been elucidated, to a certain extent, by the submitted data from the non-clinical pharmacokinetic studies.

3.(iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

The following toxicity studies of esflurbiprofen were conducted: Single-dose toxicity studies, repeat-dose toxicity studies, a carcinogenicity study (medium-term skin carcinogenicity study in mice), genotoxicity studies, reproductive and developmental toxicity studies, local tolerance studies, and other toxicity studies (e.g., study on the mechanism of toxicity). Systemic carcinogenicity of esflurbiprofen was evaluated based on the findings with FP.

No new toxicity study was conducted for the effect of mentha oil on the skin, for the following reasons: (a) There are prescription and OTC drugs containing mentha oil (as an active ingredient) at a concentration similar to that in the Loqoa Tape; these drugs have been approved and used for many years for the treatment of arthralgia, etc.; (b) no toxicity was suggested in the results from testing of the vehicle (including mentha oil) in repeat-dose toxicity studies in rats, local tolerance studies, skin sensitization studies, or other toxicity studies (phototoxicity and skin photosensitization studies), or in the literature on peppermint oil.[3]

In the toxicity studies presented below, plasters were used for dermal application and 0.5% CMC-Na solution was used as vehicle in subcutaneous administration, unless otherwise specified.

3.(iii).A.(1) Single-dose toxicity

3.(iii).A.(1).1) Dermal toxicity study in rats (4.2.3.1-01)

Esflurbiprofen (10, 30, and 60 mg/kg) was applied dermally as a single dose to Sprague Dawley (SD) rats for 24 hours. No abnormality was observed. The approximate lethal dose was determined to be >60 mg/kg.

3.(iii).A.(1).2) Dermal toxicity study in dogs (4.2.3.1-02)

Esflurbiprofen (5.25, 10.5, and 21 mg/kg) was applied dermally as a single dose to beagle dogs for 24 hours. No death occurred. All dose groups showed vomiting and soft feces. The ≥10.5 mg/kg groups showed muddy stools, mucous stools, bloody stools, and occult bleeding test positive. The 21 mg/kg group showed decreased food consumption, increased white blood count accompanied by increased ratio of segmented neutrophils, decreases in serum phosphate, calcium, albumin, and A/G ratio. Based on the above, the approximate lethal dose was determined to be >21 mg/kg.

3.(iii).A.(2) Repeat-dose toxicity

Repeat-dose dermal toxicity studies were conducted in rats (up to 6 months) and in dogs (up to 12 months). The applicant concluded that, in both rats and dogs, the toxicological target organs were the gastrointestinal tract (the stomach or small intestine) and the kidney, and that the toxicological findings observed in the studies were those common to NSAIDs (i.e., changes associated with suppression of PG production caused by COX inhibition). Atrophy of the external granular layer of the retina was observed in rats following 6 months of treatment; the applicant explained that this finding was a light-induced change specific to albino rats. In animals receiving a long-term treatment with esflurbiprofen at the no observed adverse effect level (NOAEL) (0.1 mg/kg/day in male rats, 0.3 mg/kg/day in female rats; 0.03 mg/kg/day in male dogs, and 0.1 mg/kg/day in female dogs), plasma esflurbiprofen exposure ($AUC_{0\text{-}24h}$) was less than 1 times that in humans receiving repeated application of 2 plasters of 40 mg esflurbiprofen.[4]

Toxicity of mentha oil was evaluated by a comparison between the no-treatment group and the vehicle group in a repeat-dose toxicity study in rats (up to 6 months). The study showed that mentha oil had no toxic effect.

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[3] Peppermint oil contains menthol at a concentration similar to that in mentha oil (menthol is the main ingredient of mentha oil). Peppermint oil also contains other ingredients of mentha oil (e.g., menthone, menthyl acetate).

[4] Plasma esflurbiprofen exposure ($AUC_{0\text{-}23h}$, 47,000 ng·h/mL) in Japanese healthy adults receiving 7-day repeated application of 2 plasters of SFPP-3, a formulation for clinical studies.

3.(iii).A.(2).1) Three-month repeat-dose toxicity study with a 4-week recovery period in rats (4.2.3.2-04)

Esflurbiprofen (0 [no treatment or vehicle], 1, 3, or 10 mg/kg/day) was applied dermally to SD rats for 3 months (including the period for evaluation of recovery). Death occurred in 2 of 16 males and 4 of 16 females in the 10 mg/kg group. The deceased animals showed reddish urine, blackish feces, no-defecation, decreased motility, emaciation and soiled fur, ascites retention and adhesion of gastrointestinal tract/organs, effect on gastrointestinal tract (e.g., stomach erosion/ulcer, perforated ulcer in the jejunal and ileal), effect on the kidney (e.g., swelling, necrosis of renal papillary tip, calcinosis in renal papilla, necrosis and calcinosis of renal cortical tubules), swollen, red/dark red discoloration, and haemorrhage in the adrenal gland, and atrophy of thymus.

Surviving animals showed the following findings:
The ≥1 mg/kg groups: reduction in body weight gain, effect on stomach (e.g., erosion/ulcer of glandular stomach and submucosal infiltration of inflammatory cells), and effect on the kidney (e.g., congestion of renal papilla, necrosis of renal papillary tip, swelling of collecting duct epithelium, edematous change of interstitium, and tubular dilatation);
The ≥3 mg/kg groups: reddish urine and increased water consumption;
The 10 mg/kg group: decreased food consumption, blackish feces, decreased defecation, no-defecation, effects on red blood cell parameters (decreases in red blood cell count, hemoglobin, and hematocrit), increased white blood cell count associated with increased ratio of segmented neutrophils, abnormalities in clinical chemistry (e.g., increased plasma urea nitrogen, decreased plasma total protein, and decreased plasma albumin), abnormalities in urinalysis (e.g., occult blood, protein, and squamous cells), occult bleeding test positive, increased spleen weight, increased kidney weight, decreased thymic weight, organ adhesion in the peritoneum and saccular nodes in the peritoneum, effects on the jejunum and ileum (e.g., adhesion, dark brown nodes, ulcerous/regenerating epithelium, necrosis, and fibrous thickening of the capsule), and swelling of mesenteric lymph nodes.

Animals assessed for recovery continuously showed the following findings:
The 3 mg/kg group: effects on the kidney (e.g., necrosis of renal papillary tip and basophilic epithelium of renal tubules);
The 10 mg/kg group: reddish urine, decreased red blood cell count, abnormalities in urinalysis, and organ adhesion within the peritoneal cavity.
The findings observed in renal tubules (basophilic epithelium and dilatation) and effects on the gastrointestinal tract were reversible. Based on the above, the NOAEL was determined to be <1 mg/kg/day.

The vehicle group showed decreased body weight, decreased thymic weight, and suppressed increase of glandular gastric ulcers. According to the applicant, these changes were toxicologically insignificant, because they were within the range of the historical data in the laboratory, and were probably related to stresses associated with the administration procedure.

3.(iii).A.(2).2) Three-month repeat-dose toxicity study in rats (Additional low-dose study, 4.2.3.2-05)

Esflurbiprofen (0 [no treatment or vehicle], 0.03, 0.1, or 0.3 mg/kg/day) was applied dermally for 3 months to SD rats. No abnormalities were observed in the esflurbiprofen groups, and the NOAEL was determined to be 0.3 mg/kg/day for both males and females.

3.(iii).A.(2).3) Six-month repeat-dose toxicity study in rats (4.2.3.2-06)

Esflurbiprofen (0 [no treatment or vehicle], 0.1, 0.3, or 1 mg/kg/day) was applied dermally for 6 months to SD rats. Males in the ≥0.3 mg/kg groups and females in the 1 mg/kg group showed urine protein and effects on the kidney (necrosis of renal papillary tip, hypertrophy of collecting duct epithelium of renal papilla, and edematous change of renal papillary interstitium). Males and females in the 1 mg/kg group showed reddish urine, abnormalities in urinalysis (e.g., occult blood and increased ketone bodies), effects on glandular stomach (petechiae and erosion), and increased frequency and severity of atrophy of the external granular layer of the retina. Based on the above, the NOAEL was determined to be 0.1 mg/kg/day for males and 0.3 mg/kg/day in females.

3.(iii).A.(2).4) Three-month repeat-dose toxicity study with a 4-week recovery period in dogs (4.2.3.2-08)

Esflurbiprofen (0 [vehicle], 0.1, 0.3, or 1 mg/kg/day) was applied dermally to beagle dogs for 3 months (including the period for evaluation of recovery). The ≥0.3 mg/kg groups showed increased water consumption, effects on red blood cell parameters (decrease in red blood cell count, hemoglobin, and hematocrit), clinical chemistry abnormalities (e.g., decreased serum total protein and decreased serum potassium), occult bleeding test positive, and effects on the kidney[5] (edematous change of interstitium, hypertrophy of collecting ducts, and hyperplasia of renal papillary epithelium). The 1 mg/kg group showed decreased body weight, increased white blood cell count accompanied by increased ratio of segmented neutrophils, increased frequency of bloody stool, decreased thymic weight, effects on the stomach (dark reddish macules, erosion, epithelial degeneration, and interstitial fibrosis at the pyloric region of the stomach), thymic atrophy, and decreased cortical lymphocyte count in thymus. Animals evaluated for recovery following treatment with ≥0.3 mg/kg esflurbiprofen continuously showed edematous change of interstitium in the kidney, which tended to improve compared with the symptoms at the end of the treatment period. Based on the above, the NOAEL was determined to be 0.1 mg/kg/day for both males and females.

3.(iii).A.(2).5) Twelve-month repeat-dose toxicity study in dogs (4.2.3.2-09)

Esflurbiprofen (0 [vehicle], 0.03, 0.1, or 0.3 mg/kg/day) was applied dermally to beagle dogs for 12 months. The ≥0.03 mg/kg groups showed effects on the skin at the application site (e.g., papulae and swelling). Males receiving ≥0.1 mg/kg and females receiving 0.3 mg/kg showed effect on the kidney (e.g., hyperplasia of renal papillary epithelium). The 0.3 mg/kg group showed effects on the stomach (disseminated petechiae in the gastric mucosa and granulation tissue in the lamina propria of the pyloric region). The applicant explained that the findings in the skin at the application site were unlikely to be due to esflurbiprofen for the following reasons: (a) The frequency or severity of the skin findings (e.g., papulae and swelling) were not clearly correlated with esflurbiprofen dose; (b) histopathological findings (e.g., acanthosis and monocyte infiltration) were observed in the affected skin, but no clear evidence has been found for the relationship between the skin findings and the histopathological findings. Based on the above, the NOAEL was determined to be 0.03 mg/kg/day for males and 0.1 mg/kg/day for females.

3.(iii).A.(3) Genotoxicity (4.2.3.3.1-01 to 4.2.3.3.1-02, 4.2.3.3.2-01)

The applicant conducted genotoxicity studies on esflurbiprofen: an *in vitro* bacterial reverse mutation assay, a chromosomal aberration assay using Chinese hamster lung-derived fibroblasts, and an *in vivo* micronucleus assay in mice. All tests were negative, and the applicant concluded that esflurbiprofen was not genotoxic.

3.(iii).A.(4) Carcinogenicity

Although systemic carcinogenicity studies of esflurbiprofen were not conducted, the applicant has concluded that esflurbiprofen had low risk of systemic carcinogenesis, for the following reasons:

- Esflurbiprofen is not genotoxic.
- In the long-term repeated dermal toxicity studies (6 months in rats, 12 months in dogs), no precancerous lesion was observed in any of the organs.
- After dermal application of esflurbiprofen, tissue esflurbiprofen concentrations remained lower than the plasma esflurbiprofen concentrations, except for the skin at the application site and the cutaneous muscle beneath the application site. This suggests that esflurbiprofen is unlikely to accumulate in any specific tissues [see "3.(ii).A.(2).1) Tissue distribution"].
- FP, the racemate of esflurbiprofen, was not tumorigenic in the oral carcinogenicity study. The estimated plasma esflurbiprofen exposure ($AUC_{0\text{-}24h}$), calculated from the estimated plasma FP

[5] Animals in the 1 mg/kg group showed hyperplasia of renal pelvic epithelium and hypertrophy of the epithelium of renal tubules in the pars recta.

exposure, was probably similar to the plasma esflurbiprofen exposure following application of 2 plasters of 40 mg esflurbiprofen [see "4.(ii) Summary of clinical pharmacology studies"].

Esflurbiprofen concentration at the application site reaches a high level following application of esflurbiprofen, and esflurbiprofen may be used over a long term in clinical practice. Therefore, a medium-term skin carcinogenicity study was conducted in mice to evaluate skin carcinogenicity. In this study, esflurbiprofen was not shown to promote carcinogenesis in the skin. Also, the study on the tissue distribution of esflurbiprofen in pigmented rats did not show any specific distribution in melanin-containing tissues [see "3.(ii).A.(2).1) Tissue distribution"]. In addition, the 12-month repeated dermal toxicity study in dogs did not show proliferative changes in brown pigment-containing cells in the epidermis or hair follicles at the application site. Based on the above, the applicant concluded that esflurbiprofen is unlikely to raise concerns regarding dermal carcinogenicity in long-term use.

3.(iii).A.(4).1) Medium-term skin carcinogenicity study in mice (4.2.3.4-01)

A carcinogenic initiator 7, 12-dimethylbenz[α]anthracene was applied as a single dose to the skin of ICR mice. At 7 days after application, the animals began to receive a 19-week dermal application of (a) esflurbiprofen (0% [vehicle], 2.31%, 6.93%, and 11.55% [corresponding to 0, 0.347, 1.040, and 1.733 mg/body of esflurbiprofen, respectively]) once daily or (b) a positive control (12-*O*-tetradecanoylphorbol-13-acetate) twice a week. In the 6.93% and 11.55% groups, death[6] due to systemic toxicity occurred from the first week of the test substance administration, therefore the concentration of esflurbiprofen was reduced to 4.62% (corresponding to 0.693 mg/body) in both groups.[7] Since deaths occurred even after the dose reduction, treatment was suspended for 3 weeks, after which treatment was continued with a reduced concentration of 2.77% (corresponding to 0.416 mg/body). The number of surviving animals at the end of the treatment was 19 animals in the vehicle group, 10 animals in the esflurbiprofen 2.31% group, 4 animals in the 6.93%/4.62%/2.77% (medium concentration) group, 2 animals in the 11.55%/4.62%/2.77% (high concentration) group, and 20 animals in the positive control group. Squamous papilloma and other abnormalities were observed in the skin of animals in the positive control group, whereas no tumor was observed in the skin of animals in the 2.31% group.[8] This suggested that esflurbiprofen was not carcinogenic. No skin tumor was observed even in animals in the medium and high concentration groups that survived until the end of treatment.

3.(iii).A.(5) Reproductive and developmental toxicity

The applicant conducted a study of fertility and early embryonic development to implantation in rats, embryo-fetal development studies in rats and rabbits, and studies of effects on pre- and postnatal development, including maternal function in rats.

Findings in the study of fertility and early embryonic development included decreased corpora lutea count and decreased number of implantation, and findings in the study of effects on pre- and postnatal development included delayed delivery, reduced number of deliveries, and increased number of stillbirth. Similar findings were reported with other NSAIDs (Nakane S et al, ed. *Practical guides for toxicity tests 15, Principles for safety evaluation of medical drugs* [in Japanese]. 1990:129-32, Masuzawa K et al, ed. *Practical guides for toxicity tests 15, Principles for safety evaluation of medical drugs* [in Japanese]. 1990:99-110), and the applicant explained that these findings were due to the suppression of PG production associated with COX inhibition by esflurbiprofen. The embryo-fetal development studies did not show any effect on the fetal morphology in either rats or rabbits. The plasma esflurbiprofen exposure ($AUC_{0\text{-}24h}$) at the NOAEL for embryo-fetal development (3 mg/kg/day in rats; 10 mg/kg/day in rabbits) was approximately 2.5 times (rats) and approximately 2.6 times (rabbits) that in humans receiving 2 plasters of 40 mg esflurbiprofen. The study of effects on pre- and postnatal development revealed toxic findings in maternal animals and the offspring at some doses of esflurbiprofen, and the plasma esflurbiprofen exposure ($AUC_{0\text{-}24h}$) in maternal animals given the doses was less than 1 times the exposure in humans receiving 2 plasters of 40 mg esflurbiprofen. According to the applicant, "women in late pregnancy" will be included under the Contraindications section of the package insert.

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6 The deceased animals showed pallor, abdominal distension, emaciation, decreased body temperature, decreased activity, bradypnea, gastrointestinal perforation, etc. These toxicity findings were probably due to the pharmacological action of esflurbiprofen.

7 In the 11.55% group, esflurbiprofen concentration was reduced to 4.62% after a 2-day recovery period.

8 Data from the medium and high concentration groups were not evaluated because the number of animals in the groups was too small to qualify for statistical analysis.

3.(iii).A.(5).1) Study of fertility and early embryonic development to implantation in rats (4.2.3.5.1-01)

Esflurbiprofen (0 [vehicle], 0.3, 1, or 3 mg/kg/day) was administered subcutaneously to male SD rats (from 4 weeks before mating, throughout the mating period, until the day before necropsy) and to female SD rats (from 2 weeks before mating, throughout the mating period, until Gestation Day 7). Findings in parental animals in the 3 mg/kg group were reduced body weight gain (males only), reduced food consumption (females only), and decreased corpora lutea count. The number of live early embryos decreased in the ≥1 mg/kg groups. The applicant explained that the decreased number of live embryos in the 1 mg/kg group was an incidental change, for the following reasons: (a) The number of live embryos was only slightly below the historical data in study sites[9]; (b) there was no correlation between the corpora lutea count and the number of implantations; and (c) the change was associated with the increasing tendency of postimplantation mortality. According to the applicant, the decreased number of live embryos in the 3 mg/kg group was associated with decreased corpora lutea count caused by abnormal ovulation due to suppressed PG production, and therefore the finding was not caused by direct effects on the early embryos. Based on the above, the NOAEL was determined to be 1 mg/kg/day for general and reproductive toxicity in parental animals and 3 mg/kg/day for early embryonic development.

3.(iii).A.(5).2) Embryo-fetal development study in rats (4.2.3.5.2-01)

Esflurbiprofen (0 [vehicle], 0.3, 1, or 3 mg/kg/day) was administered subcutaneously to pregnant SD rats from Gestation Day 7 to Gestation Day 17. Death[10] occurred in 1 of 20 maternal animals in the 3 mg/kg group. In the 3 mg/kg group, an increase in placental weight was observed, but the finding did not affect the maintenance of pregnancy or embryos/fetuses, therefore the applicant explained that the finding was toxicologically insignificant. Based on the above, the NOAEL was determined to be 1 mg/kg/day for the maternal general toxicity and 3 mg/kg/day for maternal reproductive toxicity and embryo-fetal development.

3.(iii).A.(5).3) Embryo-fetal development study in rabbits (4.2.3.5.2-03)

Esflurbiprofen (0 [vehicle], 3, 10, or 30 mg/kg/day) was administered subcutaneously to pregnant JW rabbits from Gestation Day 6 to Gestation Day 18. Findings observed in maternal animals were death[11] (1 of 18 animals) in the 30 mg/kg group and abortion (1 of 18 animals) in the 10 mg/kg group. Reduced body weight gain was observed in the ≥10 mg/kg groups, and decreased defecation, reduced food consumption, oliguria, and erosion and needle-like haemorrhagic spots in the stomach were observed in the 30 mg/kg group. In embryos and fetuses, the number of early resorptions increased in the 30 mg/kg group. According to the applicant, the abortion in the 10 mg/kg group was due to reduced body weight gain caused by reduced or no food consumption. Based on the above, the NOAEL was determined to be 3 mg/kg/day for maternal general toxicity and 10 mg/kg/day for maternal reproductive toxicity and embryo/fetal toxicity.

3.(iii).A.(5).4) Study on effects on pre- and postnatal development, including maternal function in rats (Preliminary study; 4.2.3.5.3-01)

Esflurbiprofen (0 [vehicle], 0.1, 0.3, 1, or 3 mg/kg/day) was administered subcutaneously to pregnant SD rats from Gestation Day 17 to Lactation Day 4. Death and moribund sacrifice occurred in maternal animals in the ≥0.1 mg/kg groups (death: 1 of 8 animals in the 0.1 mg/kg group, 1 of 8 animals in the 0.3 mg/kg group, 2 of 8 animals in the 1 mg/kg group, 3 of 8 animals in the 3 mg/kg group) (moribund sacrifice[12]: 1 of 8 animals in the 0.1 mg/kg group, 2 of 8 animals in the 0.3 mg/kg group, 4 of 8 animals in the 1 mg/kg group, 3 of 8 animals in the 3 mg/kg group). These animals showed abnormal clinical signs (e.g., vaginal haemorrhage, pale auricles, respiratory irregularity, and decrease in activity). In moribund-sacrificed animals, death of all offspring was observed in the 0.1 and 0.3 mg/kg groups, and abnormal parturition (incomplete parturition and prolongation of parturition) was observed in the ≥1 mg/kg groups. The applicant explained that these abnormalities were caused by parturition disorder

[9] In 11 studies conducted between [redacted] and [redacted], the mean number of surviving embryos per study was 13.6 to 16.2 (mean, 14.8).

[10] Decreased food consumption, emaciation, abdominal distension, retention of ascites, small intestinal ulcer perforation, etc., were observed.

[11] Decreased food consumption, perforation and thinning of gastric wall, intussusception, etc., were observed.

[12] In the moribund-sacrificed animals in the 0.1 and 0.3 mg/kg groups, all offspring died, with consequent increase in the number and the rate of stillbirth.

associated with esflurbiprofen-induced suppression of PG production. In addition, dark brown spots[13] in the glandular stomach were observed in the ≥1 mg/kg groups, and reduced food consumption and a trend of reduced body weight gain were observed in the 3 mg/kg group. In the offspring (F_1), a trend of increased number and rate of stillbirth was observed in the ≥0.1 mg/kg groups (except for the 1 mg/kg group), and a decrease or decreasing trend in the number of live offspring and live birth index was observed in the ≥0.3 mg/kg groups. Based on the above, the NOAEL was determined to be 0.3 mg/kg/day for maternal general toxicity and <0.1 mg/kg/day for maternal reproductive toxicity and offspring (F_1) toxicity.

3.(iii).A.(5).5) Study on effects on pre- and postnatal development, including maternal function in rats (Main study 4.2.3.5.3-02)

Esflurbiprofen (0 [vehicle], 0.3, 1, or 3 mg/kg/day) was administered subcutaneously[14] to pregnant SD rats from Gestation Day 7 to Lactation Day 20. Death and moribund sacrifice occurred in maternal animals in the ≥1 mg/kg groups (death: 1 of 22 animals in the 1 mg/kg group, 4 of 22 animals in the 3 mg/kg group) (moribund sacrifice: 1 of 22 animals in the 1 mg/kg group, 5 of 22 animals in the 3 mg/kg group). These animals showed vaginal haemorrhage and abnormal parturition (death of all offspring, delayed parturition, and incomplete parturition), etc.[15] Findings observed in surviving maternal animals were prolonged gestation in the ≥1 mg/kg groups and reduced food consumption, reduced body weight gain, retention of content in the gastrointestinal tract, enlargement of the mesenteric lymph nodes and the spleen, and atrophy of the thymus in the 3 mg/kg group. The offspring (F_1) in the 3 mg/kg group showed a decreasing trend in the number of newborns and live birth index, an increased number of stillbirth, reduced body weight gain, and delayed early behavioral ontogeny (dorsal righting reflex). Based on the above, the NOAEL was determined to be 1 mg/kg/day for maternal general toxicity and offspring (F_1) toxicity and 0.3 mg/kg/day for the maternal reproductive toxicity.

3.(iii).A.(6) Local tolerance studies

3.(iii).A.(6).1) Primary skin irritation studies in rabbits (4.2.3.6-01, 4.2.3.6-02)

SFPP-1 containing esflurbiprofen (0 [vehicle], 10, or 20 mg) (a formulation for clinical studies), 2% ketoprofen plaster, or adhesive plaster was occlusively applied to the back of JW rabbits (intact or injured skin) for 24 hours. Skin reaction was evaluated according to Draize criteria. As a result, esflurbiprofen was classified as a slight irritant. No significant difference was observed in skin reactions between esflurbiprofen and vehicle, 2% ketoprofen plaster, or adhesive plaster; all were classified as slight irritants.

The proposed formulation[16] (SFPP-4 containing 0 [vehicle], 10, 20, or 40 mg esflurbiprofen) or a formulation for clinical studies (SFPP-3 containing 0 [vehicle], 10, 20, or 40 mg esflurbiprofen) was occlusively applied to the back of NZW rabbits (intact and injured skin) for 24 hours. Skin reaction was evaluated according to Draize criteria. No significant difference was observed in skin reactions between SFPP-3 (including vehicle) and SFPP-4 (including vehicle); both formulations were classified as slight irritants.

3.(iii).A.(6).2) Cumulative skin irritation study in rabbits (4.2.3.6-03)

SFPP-1 containing esflurbiprofen (0 [vehicle], 10, or 20 mg) (a formulation for clinical studies), 2% ketoprofen plaster, or adhesive plaster was occlusively applied to the back of JW rabbits (intact skin) for 24 hours daily for 14 days. Esflurbiprofen was classified as a mild cumulative irritant, based on the evaluation of skin reactions according to Draize criteria and on histopathological findings (subcutaneous haemorrhage, infiltration of inflammatory cells, acanthosis). No significant difference was observed either in skin reactions or histopathological findings between SFPP-1 (including vehicle) and adhesive plaster; the applicant explained that the irritation observed in the esflurbiprofen groups was caused by the peeling procedure.

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[13] Dark brown spots were observed in 1 dead animal in the 0.1 mg/kg group as well.

[14] In order to allow evaluation of the offspring, treatment was suspended from Gestation Day 20 to Lactation Day 0 (completion of delivery). Effect on the perinatal period was evaluated based on the results of the preliminary study.

[15] Necropsy findings included atrophy of the spleen and thymus in the ≥1 mg/kg groups and dark red foci in the stomach in the 3 mg/kg group.

[16] [redacted]

3.(iii).A.(6).3) Skin sensitization studies in guinea pigs

(a) Adjuvant and patch test (4.2.3.6-04)

Emulsified Freund's complete adjuvant (FCA) was administered subcutaneously to the back of Hartley guinea pigs, followed by a primary sensitization to SFPP-1 (0 [vehicle] or 20 mg) or a positive control (>1% 1-chloro-2,4-dinitrobenzene [DNCB]) (these substances were applied once daily for 3 days) and a secondary sensitization (at 6 days after the start of sensitization, 10% sodium lauryl sulfate was applied to the site of the primary sensitization, followed by a 48-hour application of vehicle, SFPP-1, or the positive control). At 20 days after the start of the primary sensitization, animals were challenged by a-24 hour application of vehicle and SFPP-1 (in unsensitized animals and animals sensitized to vehicle or SFPP-1; vehicle was applied to an area of the skin on the back and SFPP-1 to another area, both different from the sensitized area) or of 0.1% DNCB (in animals sensitized to the positive control; DNCB was applied to an area of the skin on the back, different from the sensitized area). As a result, similar skin reactions were observed in vehicle-sensitized animals and SFPP-1-sensitized animals, suggesting that the skin sensitization was induced by vehicle.

(b) Buehler test (4.2.3.6-05)

Adjuvant and patch test showed strong skin reactions in vehicle- or SFPP-1-sensitized animals compared with unsensitized animals, suggesting the skin-sensitizing potential of esflurbiprofen plaster. Therefore, additional evaluation was conducted using a Buehler test, a testing method carried out under conditions similar to clinical settings.

Hartley guinea pigs were sensitized to SFPP-1 0 mg (unsensitized or vehicle), SFPP-1 20 mg, a comparator (2% ketoprofen plaster), or a positive control (1% DNCB). (These substances were applied to the left abdomen for 24 hours daily, 3 times a week, for 3 weeks.) At 14 days after the final sensitization, animals were challenged by a 24-hour application of the following substances to the skin of the back: (a) vehicle, SFPP-1 20 mg, the comparator, and 0.1% DNCB (in unsensitized animals); (b) vehicle and SFPP-1 20 mg (in vehicle- or SFPP-1-sensitized animals); (c) 2% ketoprofen plaster (in comparator-sensitized animals); or (d) 0.1% DNBC (in positive control-sensitized animals). Skin reaction was evaluated at 24, 48, and 72 hours after the challenge, and histopathological examination was performed at 72 hours after the challenge. Animals sensitized to vehicle or SFPP-1 20 mg showed slight to mild erythema, hyperkeratosis, thickening, inter- and intracellular oedema and degeneration of basal cells in the epidermis, and vasodilation and lymphocyte infiltration in the dermis. No significant difference was observed in the frequency or severity of these findings among the challenging substances either in vehicle-sensitized animals or SFPP-1-sensitized animals. The applicant explained that similar skin reactions were observed in the primary skin irritation study in rabbits (4.2.3.6-01), and that these reactions were caused by the primary irritation effect of SFPP-1 and vehicle. The applicant also considered that the ingredients of vehicle, including mentha oil, are unlikely to induce skin sensitization[17] and therefore SFPP-1 is unlikely to induce skin sensitization.

3.(iii).A.(7) Other toxicity studies

3.(iii).A.(7).1) Mechanistic studies

Effect on electroretinogram in dogs (Reference; 4.2.3.7.3-01)

Esflurbiprofen (0 [vehicle], 0.3, 1, or 3 mg/kg/day) was applied dermally to beagle dogs for 1 month, to investigate the effect on the visual function (including evaluation of recovery after a 14 day-recovery period). Neither ophthalmological examination nor electroretinography revealed any abnormality. Dogs given ≥0.3 mg/kg showed findings similar to those observed in the rats and dogs in the repeat-dose toxicity studies (i.e., effects on the gastrointestinal tract and related abnormalities in hematology/clinical chemistry). Dogs given 3 mg/kg showed no effect in the retina; the plasma exposure to unchanged esflurbiprofen in these dogs was 14.8 times (males) and 5.1 times (females) the exposure in rats given esflurbiprofen 1 mg/kg that showed increased frequency of the atrophy of the external granular layer of the retina in the 6-month repeat-dose toxicity study.

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17 [redacted]. Polyisobutylene, styrene-isoprene-styrene block copolymer, ester gum HG, liquid paraffin, propylene glycol dicaprylate, and dibutylhydroxytoluene were within the range of the maximum dose used in topical OTC drugs (Pharmaceutical Excipients Dictionary 2007, edited by Japan Pharmaceutical Excipients Council). [redacted].

3.(iii).A.(7).2) Evaluation of the toxicity of impurities

Impurities A and B, for which the acceptance criterion was set at a level exceeding the qualification threshold stipulated in "Revision of the Guidelines on Impurities in New Drug Products" (PFSB/ELD Notification No. 0703004 dated July 3, 2006, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW), were subjected to a 14-day repeat-dose toxicity study in rats, a bacterial reverse mutation assay, and a chromosomal aberration assay using human peripheral lymphocytes. Also, a degradation product detected after photoirradiation[18] (Photodegradation Product A) was subjected to a 14-day repeat-dose toxicity study in rats.

(a) Fourteen-day repeat-dose toxicity study of Impurity A (4.2.3.7.6-01)

SD rats received a 14-day dermal application of a formulation containing esflurbiprofen and Impurity A [redacted]% (the stressed formulation), a formulation containing esflurbiprofen and Impurity A [redacted]%, (the proposed formulation 1), or a blank formulation (containing Impurity A at doses of 0, 0.003, 0.009, 0.03, 0.043, 0.129, or 0.43 mg/kg/day). The toxicity profiles did not differ between the stressed formulation and the proposed formulation 1, whereas toxic findings tended to be severer with the proposed formulation 1. The applicant thus considered that Impurity A was not toxic.

(b) Fourteen-day repeat-dose toxicity study of Impurity B (4.2.3.7.6-04)

SD rats received a 14-day dermal application of a formulation containing esflurbiprofen and Impurity B [redacted]% or [redacted]%, (the impurity-spiked formulation), a formulation containing esflurbiprofen and Impurity B [redacted]% (the proposed formulation 2), or a blank formulation (containing Impurity B at doses of 0, 0.003, 0.03, or 0.06 mg/kg/day). No difference was observed in the toxicity profiles between the impurity-spiked formulation and the proposed formulation 2. The applicant thus considered that Impurity B was not toxic.

(c) Fourteen-day repeat-dose toxicity study of Photodegradation Product A (4.2.3.7.6-07)

SD rats received a dermal application of a formulation containing esflurbiprofen and Photodegradation Product A [redacted]% (the photo-deterioration formulation), the proposed formulation, or vehicle (containing Photodegradation Product A at doses of 0, 0.01, or 0.02 mg/kg/day) for 14 days. No difference was observed in the toxicity profiles between the photo-deterioration formulation and the proposed formulation. The applicant thus considered that Photodegradation Product A was not toxic.

(d) Genotoxicity studies (4.2.3.7.6-02 to 4.2.3.7.6-03, 4.2.3.7.6-05 to 4.2.3.7.6-06)

Impurities A and B were subjected to a bacterial reverse mutation assay and to a chromosomal aberration assay using human peripheral lymphocytes; both tests yielded negative results. The applicant thus considered that neither Impurity A nor B was genotoxic.

3.(iii).A.(7).3) Photosafety study

(a) *In vitro* phototoxicity study (Reference; 4.2.3.7.7-01)

BALB/3T3 cells were treated with 7.81 to 1000 μg/mL of esflurbiprofen, 7.81 to 1000 μg/mL (without photoirradiation) or 3.91 to 500 μg/mL (with photoirradiation) of ketoprofen, or a positive comparator (chlorpromazine hydrochloride). Phototoxicity was assessed based on the evaluation of cytotoxicity under photoirradiated and non-photoirradiated conditions. Esflurbiprofen did not inhibit cell proliferation by ≥50% at any treatment concentration regardless of photoirradiation. Thus, the applicant considered that esflurbiprofen was not phototoxic.

(b) Phototoxicity study in guinea pigs (4.2.3.7.7-02)

Vehicle, SFPP, or a positive control (1% 8-methoxypsoralen) was applied to the skin of the back of Hartley guinea pigs for 30 minutes, to evaluate skin reactions in the absence and presence of UV irradiation (approximately 10 J/cm^2). No skin reaction was observed either in the vehicle or SFPP group, regardless of UV irradiation. Based on the above, the applicant considered that neither esflurbiprofen nor vehicle had photoirritant potential.

[18] Photodegradation Product A is not classified as a degradation product generated under ordinary storage conditions stipulated in "Revision of the Guidelines on Impurities in New Drug Products."

(c) Skin photosensitization study in guinea pigs (4.2.3.7.7-03)
SFPP, vehicle, or a positive control (5% 6-methylcoumarin) was applied for 30 minutes to the skin of the back of Hartley guinea pigs, followed by UV irradiation (approximately 10 J/cm^2) once daily for 5 days. At 21 days after the start of sensitization, animals were challenged by SFPP, vehicle, or a positive control (1% 6-methylcoumarin), applied to 2 areas of the skin on the back for 30 minutes, followed by UV irradiation to 1 of the 2 areas. No skin reaction was observed either in the SFPP-sensitized animals or vehicle-sensitized animals at 24 or 48 hours after the challenge, regardless of UV irradiation. Thus, the applicant considered that neither SFPP nor vehicle has photosensitizing potential.

3.(iii).B Outline of the review by PMDA

3.(iii).B.(1) Atrophy of the external granular layer of the retina

PMDA asked the applicant to explain the relationship between treatment with esflurbiprofen and the atrophy of the external granular layer of the retina observed in the 6-month repeat-dose toxicity study in rats, and to discuss the risk of the atrophy in humans treated with esflurbiprofen.

The applicant's response:
The animals given esflurbiprofen 1 mg/kg showed increased frequency and severity of the atrophy of the external granular layer of the retina. However, albino rats are known to show spontaneous photo-induced retinal atrophy due to insufficient melanin pigment in the retinal pigment epithelium (Tanaka K et al. *Histopathology of Toxicologic Pathology* [in Japanese], edited by Japanese Society of Toxicologic Pathology. 2000;462; Kobayashi K et al. *Anim Eye Res.* 1993;13:17-28; Bellhorn RW et al. *Lab Anim Sci.* 1980;30:440-450; Perez J et al. *Exp Toxicol Pathol.* 1994;46:229-235; Kuse H et al. *Locomotor toxicity/sense organ toxicity* [in Japanese], edited by Japanese Society of Toxicology 2003;285); the histopathological images of spontaneous retinal atrophy in albino rats were similar to those of the atrophied/depleted external granular layer of the retina observed in the study. Also, spontaneous photo-induced retinal atrophy is observed at an illuminance level similar to that in the rearing environment in the laboratory that conducted the 6-month repeat-dose toxicity study (Semple-Rowland SL et al. *Lab Anim Sci.* 1987;37:289-98). The applicant considered that esflurbiprofen was not the cause of atrophy of the external granular layer of the retina observed in the study, for the following reasons: (a) animals in the high-dose group were kept in a rearing environment more susceptible to illumination exposure; (b) the positions of rearing cages were not changed during the treatment period. In the study, atrophy was observed more frequently and intensely in females than males, and female rats are known to be more sensitive to photo-induced atrophy than males (Scharden JL et al. *Lab Anim Sci.* 1975;25:323-326; Mudry MCDV et al. *Toxicol Pathol.* 2013;41:813-825). In the oral carcinogenicity studies of FP in rats (ANSAID. NDA No.018766, 1986), effects on the retina were not observed with FP at doses up to 4 mg/kg, the maximum dose tested, and the estimated esflurbiprofen exposure in the FP 4 mg/kg group ($AUC_{0\text{-}24h}$, 48.01 μg·h/mL) was 5.6 times (males) or 1.4 times (females) the plasma esflurbiprofen exposure ($AUC_{0\text{-}24h}$) in rats given 1 mg/kg esflurbiprofen (the highest dose) in the 6-month repeat-dose toxicity study. In the 12-month repeated dose toxicity study in dogs, no atrophy of the external granular layer of the retina was observed, and the plasma esflurbiprofen exposure ($AUC_{0\text{-}24h}$) in the dogs exceeded that in the rats showing atrophy of the external granular layer of the retina. Moreover, the effect of esflurbiprofen on visual function was investigated in a 1-month repeat-dose study in dogs. The plasma esflurbiprofen exposure ($AUC_{0\text{-}24h}$) in the dogs was 14.8 times (males) and 5.1 times (females) that in the rats showing atrophy of the external granular layer of the retina, and 2.7 times (males) and 3.7 times (females) that observed in clinical studies. Nevertheless, the results revealed no abnormality either in ophthalmological examination or in electroretinogram, showing no effect on visual function. The long-term clinical study of esflurbiprofen (Study SFPP-03-OA02) revealed eye-related adverse events (i.e., conjunctival haemorrhage, conjunctivitis, allergic conjunctivitis, and eyelid ptosis), but all were considered unrelated to esflurbiprofen. In addition, no adverse events suggestive of retinal atrophy have been reported in patients treated with a patch formulation of FP (the racemate of esflurbiprofen) in clinical studies, the use-results survey, or the post-marketing surveillance.

The above findings suggest that the atrophy of the external granular layer of the retina in rats is unlikely to be due to esflurbiprofen, and that the atrophy is unlikely to occur in humans with abundant melanin pigments. Also, taking account of the clinical experience with FP, the atrophy is unlikely to occur in humans in routine clinical use.

PMDA's view:
The atrophy of the external granular layer of the retina in rats given esflurbiprofen 1 mg/kg may have been due to esflurbiprofen-induced aggravation of spontaneous atrophy. However, PMDA accepts the applicant's explanation that the finding is unlikely to pose a safety concern in humans treated with esflurbiprofen, in view of the pathological background (i.e., spontaneous atrophy is specific to albino rats) and of the clinical experience with FP, the racemate of esflurbiprofen.

4. Clinical data

4.(i) Summary of biopharmaceutic studies and associated analytical methods

4.(i).A Summary of the submitted data

The applicant conducted clinical studies using the esflurbiprofen formulations for clinical studies (SFPP-1, SFPP-2, SFPP-3) and the proposed formulation (SFPP-4), and submitted results of the following studies: (a) Comparison of pharmacokinetics between SFPP-1 and SFPP-2 (5.3.3.1-05); (b) *in vitro* bioequivalence between SFPP-3 and SFPP-4 (3.2.P.2.2-05, 4.2.2.2-07); and (c) dose relationship of each formulation (5.3.5.3-01). Unchanged esflurbiprofen and its metabolites (conjugates of unchanged esflurbiprofen; M1, M2, M3, and M4; and conjugates of M1, M2, and M3) in plasma, urine, synovial membrane, and synovial fluid were measured by high-performance liquid chromatography-fluorescence detection (HPLC-FL) or by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (lower limit of quantitation, 2 ng/mL [HPLC-FL] or 0.5 ng/mL [LC-MS/MS] for unchanged esflurbiprofen in plasma; 5 ng/mL [HPLC-FL] for unchanged esflurbiprofen in urine; 5 ng/g [LC-MS/MS] for unchanged esflurbiprofen in synovial membrane; 0.5 ng/mL [LC-MS/MS] for unchanged esflurbiprofen in synovial fluid; 20 ng/mL [HPLC-FL] for M1-M4 in plasma; 100 ng/mL [HPLC-FL] for M1-M4 in urine).

In this section, pharmacokinetic parameters are expressed in mean or mean ± SD, unless otherwise specified.

Formulations used in clinical studies

Formulation	Clinical studies	Changes from the previous formulation
SFPP-1	Skin safety study, single application study, repeated application study (a)	
SFPP-2	Repeated application study (b), Japanese early phase II study (Study 02-OA01)	[redacted]
SFPP-3	Japanese late phase II study (a) (Study 02-OA02), Japanese phase [redacted] study ([redacted]), tissue distribution study, Japanese late phase II study (b) (Study 02-OA03), high-dose safety study	[redacted]
SFPP-4 (the proposed formulation)	Japanese phase III study (Study 03-OA01), long-term study (Study 03-OA02), PK study of the final formulation	[redacted]

4.(i).A.(1) Comparison of pharmacokinetics between SFPP-1 and SFPP-2 (5.3.3.1-04, Study 2119-03-602 [[redacted] to [redacted]]; 5.3.3.1-05, Study 2119-04-602 [[redacted] to [redacted]])

Pharmacokinetics of SFPP-1 (40 mg) and SFPP-2 (40 mg) was investigated in randomized, single-blind studies in Japanese healthy adult men (20 subjects in Study 2119-03-602, 12 subjects in Study 2119-04-602). In subjects treated with SFPP-1, C_{max}, T_{max}, and $AUC_{0\text{-}23h}$ of unchanged esflurbiprofen were 821.7 ± 302.9 ng/mL, 16.8 ± 6.9 hours, and 14,338.3 ± 5468.7 ng·h/mL, respectively, on Day 1 of treatment, and 1392.0 ± 388.6 ng/mL, 8.3 ± 2.0 hours, and 25,073.0 ± 6349.8 ng·h/mL, respectively, on Day 7. In subjects treated with SFPP-2, C_{max}, T_{max}, and $AUC_{0\text{-}23h}$ of unchanged esflurbiprofen were 877.6 ± 486.0 ng/mL, 15.0 ± 6.8 hours, and 14,718.1 ± 7276.4 ng·h/mL, respectively, on Day 1 of treatment, and 1175.6 ± 379.2 ng/mL, 8.3 ± 0.8 hours, and 20,800.0 ± 6367.7 ng·h/mL, respectively, on Day 7.

4.(i).A.(2) Studies on bioequivalence between SFPP-3 and SFPP-4

4.(i).A.(2).1) *In vitro* release test (3.2.P.2.2-05)

[redacted][19][redacted]. The esflurbiprofen release rate from SFPP-3 (40 mg) and from SFPP-4 (40 mg) was [redacted]% and [redacted]%, respectively, (mean release ratio, 1.02) at [redacted] minutes after the start of the test, [redacted]% and [redacted]%, respectively, (mean release ratio, 1.05) at [redacted] hours after the start of the test, and [redacted]% and [redacted]%, respectively, (mean release ratio, 1.09) at [redacted] hours after the start of the test. The results thus met the bioequivalence criteria for *in vitro* release test (i.e., mean release ratio of 0.8-1.2).

4.(i).A.(2).2) *In vitro* permeation test (4.2.2.2-07)

In vitro permeability of esflurbiprofen of SFPP-3 and SFPP-4 was compared using the skin of hairless rats. SFPP-3 (40 mg) or SFPP-4 (40 mg) was applied to skin specimens attached to diffusion cells (the skin specimens were isolated from the abdomen of male hairless rats), to allow esflurbiprofen to permeate through the skin. The permeation rate was [redacted]% (SFPP-3) and [redacted]% (SFPP-4) (mean permeation ratio, 1.12) at [redacted] hours after the start of the test and [redacted]% (SFPP-3) and [redacted]% (SFPP-4) (mean permeation ratio, 1.08) at [redacted] hours after the start of the test. The results thus met the bioequivalence criteria for *in vitro* testing of permeability (i.e., mean permeation ratio of 0.7-1.3).

4.(i).B Outline of the review by PMDA

The applicant's explanation:

SFPP-1, SFPP-2, SFPP-3, and SFPP-4 were used in clinical studies, but the differences between the formulations had only a minor effect on the pharmacokinetics of esflurbiprofen, for the following reasons:

- The repeated application studies (5.3.3.1-04, 5.3.3.1-05) revealed no significant differences in the pharmacokinetic parameters of unchanged esflurbiprofen between SFPP-1 and SFPP-2, suggesting that the 2 formulations had similar dermal absorption rate.

- In *in vitro* release and permeation tests of SFPP-3 and SFPP-4, the mean release and permeation ratios met the bioequivalence criteria.

- SFPP-1, SFPP-3, and SFPP-4 demonstrated dose proportionality across the dose range of 2 to 80 mg, according to the pooled data on C_{max} and $AUC_{0-\infty}$ from the single application study of SFPP-1, the high-dose safety study of SFPP-3, and the PK study of SFPP-4 (the final formulation) (5.3.5.3-01).

- The dermal absorption rates of SFPP-3 and SFPP-4 were comparable, according to the following study results:
  (a) The plasma concentration of unchanged esflurbiprofen at 12 hours postdose was 362 ± 85 ng/mL in the tissue distribution study of SFPP-3 (20 mg) and 697 ± 388 ng/mL in the PK study of the final formulation (SFPP-4, 40 mg). The ratio of SFPP-3 (20 mg) to SFPP-4 (40 mg) was thus approximately 1:2.
  (b) According to the high-dose safety study of SFPP-3 (80 mg) and the PK study of the final formulation (SFPP-4, 40 mg), C_{max} of unchanged esflurbiprofen was 1370 ± 459 ng/mL (SFPP-3, 80 mg) and 751 ± 360 ng/mL (SFPP-4, 40 mg), and $AUC_{0-\infty}$of unchanged esflurbiprofen was 35,400 ± 10,900 ng·h/mL (SFPP-3, 80 mg) and 19,000 ± 9390 ng·h/mL (SFPP-4, 40 mg). The ratio of SFPP-4 (40 mg) to SFPP-3 (80 mg) was thus approximately 2:1.

PMDA's view:

No significant differences were observed in the pharmacokinetics of esflurbiprofen among SFPP-1, SFPP-2, SFPP-3, and SFPP-4. Therefore, no specific biological consideration is required in evaluating the clinical studies conducted using different formulations.

[19] [redacted]

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

The applicant submitted results of the following studies: A PK study of the final formulation (SFPP-4, the proposed formulation) (5.3.3.1-01, SFPP-03-CP01), a long-term study of SFPP-4 (5.3.5.2-01, SFPP-03-OA02), a single application study of SFPP-1 (5.3.3.1-03, 2119-02-601), a repeated application study of SFPP-1 (5.3.3.1-04, 2119-03-602), a repeated application study of SFPP-2 (5.3.3.1-05, 2119-04-602), a high-dose safety study of SFPP-3 (5.3.3.1-06, SFPP-01-CP01), and a tissue distribution study of SFPP-3 (5.3.3.2-01, SFPP-02-LPK01). The applicant also submitted the literature on the effects on specific populations (sex, the elderly, patients with hepatic impairment, patients with renal impairment) and on the pharmacokinetic drug interactions.

4.(ii).A.(1) Pharmacokinetic studies

4.(ii).A.(1).1) Single application studies in healthy adults (5.3.3.1-01, SFPP-03-CP01 [[redacted]]; 5.3.3.1-03, 2119-02-601 [[redacted]]; 5.3.3.1-06, Study SFPP-01-CP01 [[redacted]])

In single-blind studies in healthy adult men, SFPP-1 (2, 5, 10, 20, 40, and 60 mg), SFPP-3 (80 mg), or SFPP-4 (40 mg) was applied dermally as a single dose (for 23 hours). Table 5 shows the pharmacokinetic parameters of unchanged esflurbiprofen. Following application of SFPP-1 (20 mg), glucuronide conjugate of unchanged esflurbiprofen was detected as a metabolite in plasma (C_{max}, 34.2 ± 28.0 ng/mL; $t_{1/2}$, 10.1 ± 3.6 hours; $AUC_{0\text{-}71h}$, 610.5 ± 609.9 ng·h/mL). M1 was detected only at 10 hours after the beginning of treatment (18.6 ± 15.6 ng/mL).

Table 5. Pharmacokinetic parameters of unchanged esflurbiprofen following a single dermal application of SFPP-1, SFPP-3, or SFPP-4 to Japanese healthy adults

Formulation	Dose	N	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)	$AUC_{0\text{-}\infty}$ (ng·h/mL)	CL/F (L/h)	V/F (L)	Dermal absorption rate[a)] (%)
SFPP-4 (the proposed formulation)	40 mg	7	751 ± 360	14.0 (12.0-24.0)	8.6 ± 0.6	19,000 ± 9390	-	-	48.3 ± 16.7
SFPP-1	2 mg	7	43.3 ± 7.1	10.0 (8.0-24.0)	8.3 ± 0.9	1051 ± 157	2.0 ± 0.4	37.7 ± 7.5	61.2 ± 10.7
	5 mg	7	114.5 ± 20.3	12.0 (10.0-24.0)	7.8 ± 1.2	2801 ± 414	1.8 ± 0.3	35.8 ± 8.4	68.0 ± 12.4
	10 mg	7	248.0 ± 63.5	10.0 (8.0-12.0)	7.8 ± 1.1	6056 ± 1423	1.7 ± 0.4	31.8 ± 8.6	72.2 ± 10.5
	20 mg	6	444.1 ± 120.3	13.0 (12.0-24.0)	8.4 ± 0.5	11,705 ± 3054	1.8 ± 0.4	35.1 ± 8.1	64.1 ± 10.5
	40 mg	7	858.2 ± 235.8	14.0 (10.0-24.0)	8.4 ± 1.1	23,130 ± 7855	1.9 ± 0.6	37.9 ± 11.1	57.5 ± 9.3
	60 mg	7	1188 ± 295	14.0 (12.0-24.0)	7.6 ± 0.4	30,237 ± 7430	2.1 ± 0.5	41.7 ± 11.1	51.4 ± 7.9
SFPP-3	80 mg	7	1370 ± 459	14.0 (10.0-24.0)	7.7 ± 0.3	35,400 ± 10,900	-	-	52.8 ± 14.5

Mean ± SD; T_{max} in median (minimum – maximum).
Abbreviations: C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration; $t_{1/2}$, elimination half-life; AUC, area under the plasma concentration-time curve; CL/F, total body clearance; V/F, distribution volume; -, no data;
a) Calculated from the residual amount in the formulation.

4.(ii).A.(1).2) Repeated application studies in healthy adults (5.3.3.1-04, Study 2119-03-602 [[redacted]]; 5.3.3.1-05, Study 2119-04-602 [[redacted]]; 5.3.3.1-06, Study SFPP-01-CP01 [[redacted]])

In the single-blind studies in healthy adult men, SFPP-1 (20 and 40 mg), SFPP-2 (40 mg), or SFPP-3 (80 mg) was applied dermally (once daily, 23 hours per day) for 7 days. Table 6 shows the pharmacokinetic parameters of unchanged esflurbiprofen. Following repeated application of SFPP-3 (80 mg), the urinary excretion rate (expressed as a percentage of the administered dose) remained constant from Day 4 onward. On Days 4 to 7, the urinary excretion rate up to 24 hours after the beginning of treatment was 0.27% to 0.30% for unchanged esflurbiprofen, 9.8% to 10.8% for the conjugate of unchanged esflurbiprofen, 1.3% to 1.6% for M1, and 26.1% to 30.2% for the conjugate of M1. The dermal absorption rate tended to increase with repeated application. This was probably attributable to the decreased barrier function of the keratinous layer due to repeated application and removal of plasters. In Study SFPP-03-OA02, however, no significant difference was observed in the plasma concentration

of unchanged esflurbiprofen at 4, 8, and 12 weeks after the beginning of treatment. Based on the above, the applicant explained that repeated application and removal of plasters caused thinning of the keratinous layer, resulting in decreased barrier function, but did not impair the barrier function beyond a certain level.

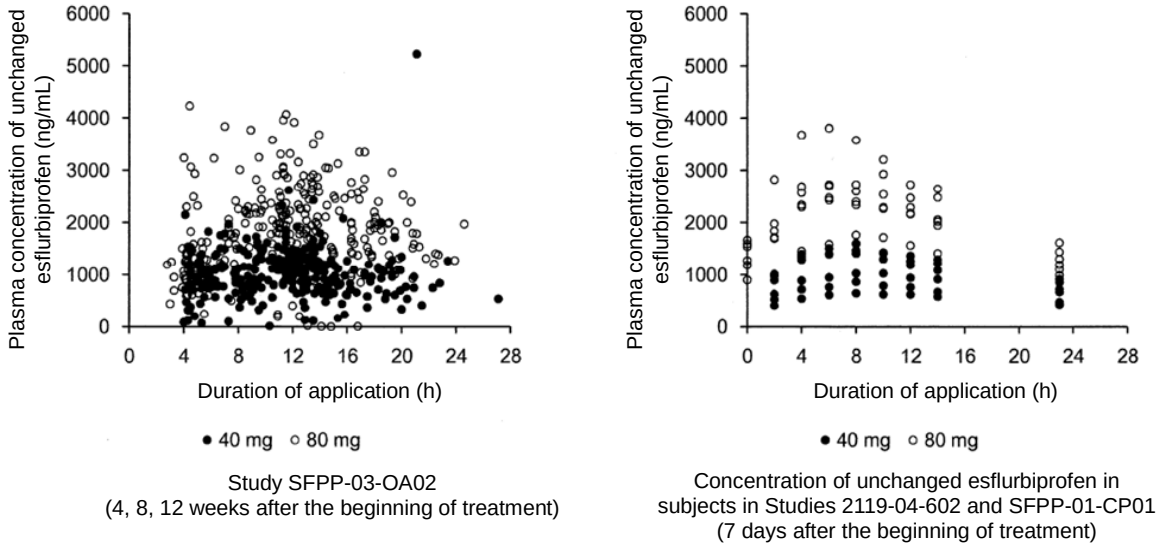
Table 6. Pharmacokinetic parameters of unchanged esflurbiprofen following 7-day repeated dermal application of SFPP-1, SFPP-2, or SFPP-3 to Japanese healthy adults

	Dose	N	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)	$AUC_{0\text{-}23h}$ (ng·h/mL)	$AUC_{0\text{-}\infty}$ (ng·h/mL)	Dermal absorption rate[a)] (%)
SFPP-1								
After the first dose	20 mg	7	493.8 ± 239.7	14.0 (6.0-23.0)	-	8333 ± 3429	-	55.6 ± 18.5
	40 mg	6	821.7 ± 302.9	17.5 (8.0-23.0)	-	14,338 ± 5469	-	52.9 ± 12.8
After the last dose	20 mg	7	880.5 ± 301.5	10.0 (4.0-23.0)	9.5 ± 3.3	14,308 ± 3905	18,565 ± 4277	71.2 ± 16.6
	40 mg	6	1392 ± 388.6	8.0 (6.0-12.0)	7.8 ± 0.5	25,073 ± 6350	32,854 ± 7493	70.8 ± 13.6
SFPP-2								
After the first dose	40 mg	6	877.6 ± 486.0	13.0 (6.0-23.0)	-	14,718 ± 7276	-	56.7 ± 18.5
After the last dose	40 mg	6	1176 ± 379.2	8.0 (8.0-10.0)	7.2 ± 0.5	20,800 ± 6368	27,027 ± 8432	70.2 ± 10.9
SFPP-3								
After the first dose	80 mg	6	1360 ± 551	10.0 (8.0-12.0)	-	23,500 ± 8530	-	54.4 ± 14.2
After the last dose	80 mg	6	2710 ± 669	6.0 (4.0-10.0)	8.1 ± 0.5	47,000 ± 10,100	59,200 ± 12,900	73.2 ± 11.6

Mean ± SD; T_{max} in median (minimum – maximum).
Abbreviations: C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration; $t_{1/2}$, elimination half-life; AUC, area under the plasma concentration-time curve; -, no data;
a) Calculated from the residual amount of drug in the formulation.

4.(ii).A.(1).3) Study in patients (5.3.5.2-01, Study SFPP-03-OA02 [[redacted] to [redacted]])

Plasma concentration of unchanged esflurbiprofen was determined in the long-term study (Study SFPP-03-OA02) in which SFPP-4 (the proposed formulation, 40 or 80 mg) was applied dermally (for 24 hours) to 201 patients with OA (including non-knee OA). Figure 2 depicts the plasma concentrations of unchanged esflurbiprofen at 4, 8, and 12 weeks after the beginning of treatment, showing no significant difference between these time points. The plasma concentration data obtained in this study were similar to those from Studies 2119-04-602 and SFPP-01-CP01, which investigated repeated dermal application of SFPP to healthy adults (Figure 2). Also, no specific difference was observed in the exposure to unchanged esflurbiprofen following application to different sites (knee joint, lumbar, or neck) (Figure 3).



Study SFPP-03-OA02
(4, 8, 12 weeks after the beginning of treatment)

Concentration of unchanged esflurbiprofen in subjects in Studies 2119-04-602 and SFPP-01-CP01
(7 days after the beginning of treatment)

Figure 2. Plasma concentration of unchanged esflurbiprofen following repeated dermal application of esflurbiprofen (40 mg, 80 mg) (Study SFPP-03-OA02)

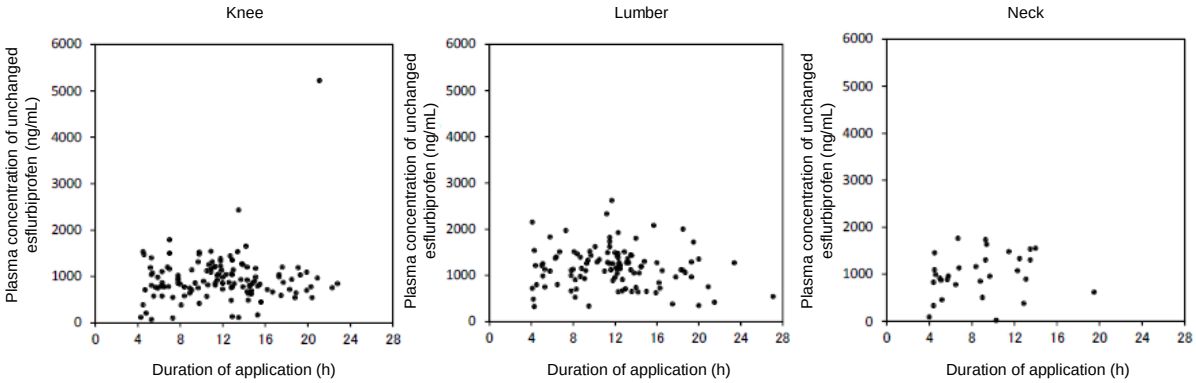


Figure 3. Plasma concentration of unchanged esflurbiprofen following repeated dermal application of esflurbiprofen (40 mg) to different sites (Study SFPP-03-OA02)

4.(ii).A.(1).4) Study on tissue distribution (5.3.3.2-01, Study SFPP-02-LPK01 [[redacted] to [redacted]])

Concentration of unchanged esflurbiprofen in joint tissues and plasma was determined following a single dermal application (for 12 hours) of SFPP-3 (20 mg) or an approved patch of flurbiprofen (FP 40 mg) to patients with knee OA scheduled to undergo artificial knee joint replacement (10 or 9 patients per group). Following a 12-hour dermal application of SFPP-3 (20 mg) or FP patch (40 mg), the concentration of unchanged esflurbiprofen in the joint at the application site was as follows: 84.5 ± 17.7 ng/g (SFPP) and 5.7 ± 0.7 ng/g (FP) in the synovial membrane; 149 ± 15.0 ng/mL (SFPP) and 4.6 ± 1.2 ng/mL (FP) in the synovial fluid; and 362 ± 26.8 ng/mL (SFPP) and 10.5 ± 3.4 ng/mL (FP) in plasma. The dermal absorption rates (mean ± standard error [SE]) were 44.5% ± 3.4% (SFPP) and 5.8% ± 0.6% (FP).

4.(ii).A.(2) Study on the effect of intrinsic factors on the pharmacokinetics of esflurbiprofen

Sections 4.(ii).A.(2).1) to 4) discuss the effect of intrinsic factors on the pharmacokinetics of esflurbiprofen following administration of Loqoa Tape. Because esflurbiprofen is the (*S*)-enantiomer of FP, the discussion is based on the literature on oral FP. Study SFPP-03-OA02 (5.3.5.2-01) did not show any significant difference in the plasma concentration of unchanged esflurbiprofen between men and women or among age groups.

4.(ii).A.(2).1) Sex (5.3.3.3-01, 5.3.3.3-02)

Following a single dose of oral FP (100 mg) to healthy adult men (18-40 years old, n = 15) and postpartum women (18-29 years old, n = 10), C_{max} of FP was 14.2 ± 4.2 (mean ± SD) and 14.7 ± 1.1 μg/mL (mean ± SE), respectively, $t_{1/2}$ was 7.4 (harmonic mean) and 5.8 hours (calculated from the elimination half-life of 0.12 ± 0.01 $hours^{-1}$), respectively, and $AUC_{0-\infty}$ was 82.7 ± 20.4 (mean ± SD) and 83.3 μg·h/mL (calculated from the total body clearance of 20 mL/min), respectively. No significant difference was observed between the men and women (Szpunar GJ et al. *Biopharm Drug Dispos.* 1987;8:273-283, Cox SR et al. *Pharmacotherapy.* 1987;7:211-215).

4.(ii).A.(2).2) The elderly (5.3.3.3-01, 5.3.3.3-03)

Following a single dose of oral FP (100 mg) to healthy adult men (18-40 years old, n = 15), elderly patients with rheumatism (65-83 years old, n = 13), and non-elderly patients with rheumatism (40-60 years old, n = 12), C_{max} of FP was 14.2 ± 4.2, 11.7 ± 3.9, and 12.7 ± 3.9 μg/mL, respectively, $t_{1/2}$ was 7.4 (harmonic mean), 6.2 ± 1.6, and 5.6 ± 1.6 hours, respectively, and $AUC_{0-\infty}$ was 82.7 ± 20.4, 58.3 ± 12.1, and 69.6 ± 23.0 μg·h/mL, respectively. No significant difference was observed among the subgroups (Szpunar GJ et al. *Biopharm Drug Dispos.* 1987;8:273-283, Kean WF et al. *J Clin Pharmacol.* 1992;32:41-48).

4.(ii).A.(2).3) Patients with hepatic impairment (5.3.3.3-04)

Following a single dose of oral FP (200 mg) to healthy adults (n = 8) and patients with alcoholic liver cirrhosis (n = 8), no significant difference was observed in the clearance of unchanged FP or (*R*)-FP or in the formation clearance of M1 between the subgroups (Blouin RA et al. *Pharm Res.* 1988;5:Suppl S220 PP1485).

4.(ii).A.(2).4) Patients with renal impairment (5.3.3.3-05, 5.3.3.3-06, 5.3.3.3-08)

Following a single dose of oral FP (50 mg) to healthy adults (n = 6) and patients with mild to moderate renal impairment (n = 8; inulin clearance, 10.5-42.8 mL/min), C_{max} of unchanged FP was 4.2 ± 1.0 and 2.7 ± 0.8 μg/mL, respectively, $t_{1/2}$ was 6.0 ± 1.4 and 5.9 ± 1.7 hours, respectively, and $AUC_{0-\infty}$ was 27.0 ± 6.7 and 15.3 ± 6.7 μg·h/mL, respectively (Knadler MP et al. *Br J Clin Pharmacol.* 1992;33:369-375, Knadler MP et al. *Br J Clin Pharmacol.* 1992;33:377-383).

Following a single dose of oral FP (100 mg) to healthy adults (n = 9) and patients with renal failure on continuous peritoneal dialysis (n = 8; creatinine clearance, <3.5 mL/min), C_{max} of unchanged FP was 7.3 ± 2.2 and 4.8 ± 1.6 μg/mL, respectively, $t_{1/2}$ was 5.3 and 3.3 hours, respectively, and $AUC_{0-\infty}$ was 41.9 ± 12.8 and 21.9 ± 10.9 μg·h/mL, respectively (Cefali EA et al. *J Clin Pharmacol.* 1991;31:808-814).

The applicant's explanation about the results:
The above data suggested that the plasma concentration of unchanged FP was lower in patients with renal impairment than in healthy adults. However, the fraction of free FP was 0.043 ± 0.007 in healthy adults and 0.092 ± 0.022 in patients with renal impairment (creatinine clearance, <10 mL/min), and patients with renal impairment have a high fraction of free FP (Blouin R et al. *Br J Clin Pharmacol.* 1993;35:62-64). These data suggest that plasma concentration of free FP is unlikely to differ greatly between patients with renal impairment and healthy adults.

4.(ii).A.(3) Studies on drug-drug interactions

4.(ii).A.(3).1) Fluconazole (5.3.3.4-01)

The effect of fluconazole, a CYP2C9 inhibitor, on the pharmacokinetics of FP following oral administration was investigated in healthy adults. Concomitant fluconazole reduced CL/F of FP, and increased $AUC_{0-\infty}$, of FP (Zgheib NK et al. *Br J Clin Pharmacol.* 2007;63:477-487).

4.(ii).A.(3).2) Methotrexate (5.4-63)

Safety of the combination of oral FP and methotrexate was investigated in patients with rheumatoid arthritis. Patients receiving methotrexate and oral FP presented with toxic symptoms (e.g., anaemia, neutrophil count decreased, platelet count decreased) supposedly due to enhanced activity of methotrexate (Frenia ML et al. *The Annals of Pharmacotherapy.* 1992;26:234-237). It was discussed

that FP-induced inhibition of prostaglandin (PG) led to decreased renal blood flow, resulting in suppression of renal excretion of methotrexate.

4.(ii).A.(3).3) Lithium carbonate (5.3.3.4-05)

The effect of concomitant oral FP on the pharmacokinetics of lithium carbonate was investigated in patients with bipolar disorder or schizoaffective disorder. FP slightly increased C_{max} and $AUC_{0\text{-}12h}$ of lithium carbonate (1.1 and 1.2 times higher, respectively) (Hughes BM et al. *Pharmacotherapy.* 1997;17:113-120). It was discussed that FP-induced inhibition of PG synthesis led to decreased renal excretion of lithium, resulting in increased blood lithium concentration.

4.(ii).A.(3).4) Furosemide (5.3.3.4-06)

The effect of concomitant oral FP on the pharmacokinetics of furosemide was investigated in healthy adults. FP slightly increased the pharmacokinetic parameters of furosemide (C_{max}, 1.2 times higher; AUC, 1.3 times higher) (Symmons DP et al. *Int J Clin Pharmacol Ther Toxicol.* 1983;21:350-354).

Concomitant FP reduces the diuretic effect of furosemide (i.e., cumulative urinary excretion, cumulative urinary Na excretion, and cumulative urinary K excretion) (Wilkins MR et al. *Int J Clin Pharmacol Ther Toxicol.* 1986;24:55-57). It was discussed that the reduced diuretic effect was caused by the retention of water and salts in the body due to FP-induced inhibition of prostaglandin (PG) synthesis.

The applicant's explanation:
The package insert for Loqoa Tape should include a precautionary statement regarding the pharmacokinetic drug interactions of esflurbiprofen (in the same manner as the package inserts for the approved oral FP products), as well as data from the submitted literature on the pharmacokinetic interactions.

4.(ii).B Outline of the review by PMDA

4.(ii).B.(1) Pharmacokinetics of esflurbiprofen and the number of esflurbiprofen plasters to be applied

The applicant's explanation about the pharmacokinetics of esflurbiprofen following application of esflurbiprofen and the maximum number of plasters to be applied:
In Study SFPP-02-LPK01, SFPP-3 (20 mg) was applied to the knee of patients with OA who were scheduled to undergo surgery. The concentrations of unchanged esflurbiprofen in the synovial membrane, synovial fluid, and plasma collected during surgery were higher than those following application of an approved FP patch; this demonstrates that esflurbiprofen is superior in dermal absorbability and distribution in deep tissues of the knees. At Day 7 of repeated application of SFPP-3 80 mg (2 plasters/day), C_{max} and $AUC_{0\text{-}23h}$ (mean ± SD) of unchanged esflurbiprofen were 2710 ± 669 ng/mL and 47,000 ± 10,100 ng·h/mL, respectively. Meanwhile, the following are the estimated C_{max} and $AUC_{0\text{-}24h}$ (mean ± SD) of unchanged FP after repeated administration of an oral FP 40 mg 3 times daily (Froben Tab. 40) or an intravenous flurbiprofen axetil[20] (FP-ax) 50 mg twice daily (Ropion Intravenous 50 mg): oral FP, 4100 ± 612 ng/mL (C_{max}) and 48,000 ± 7760 ng·h/mL[21] ($AUC_{0\text{-}24h}$); intravenous FP-ax; 5840 ± 263 ng/mL (C_{max}) and 35,000 ± 3000 ng·h/mL[22] ($AUC_{0\text{-}24h}$). Thus, the systemic exposure ($AUC_{0\text{-}23h}$) following once daily application of 2 plasters of 40 mg esflurbiprofen is comparable to the systemic exposure ($AUC_{0\text{-}24h}$) to unchanged compound following administration of oral FP at the recommended daily clinical dose; this suggests that esflurbiprofen plasters may pose a safety risk comparable to that posed by the approved oral FP and the intravenous FP-ax. The systemic exposure ($AUC_{0\text{-}24h}$) following application of ≥3 plasters of 40 mg esflurbiprofen per day, would exceed the

[20] Flurbiprofen axetil is rapidly hydrolyzed to FP after administration.

[21] The estimated C_{max} of the racemate was obtained by multiplying "C_{max} after a single dose" by "the accumulation factor calculated from $t_{1/2}$." The estimated C_{max} of esflurbiprofen was obtained by multiplying the estimated C_{max} of the racemate by 1/2. The estimated $AUC_{0\text{-}24h}$ of the racemate was obtained by multiplying "$AUC_{0\text{-}24h}$ after a single dose" by 3 (the number of doses per day). The estimated $AUC_{0\text{-}24h}$ of esflurbiprofen was obtained by multiplying the estimated $AUC_{0\text{-}24h}$ of the racemate by 1/2, based on a report on administration of oral FP (Knadler MP et al. *Br J Clin Pharmacol.* 1992;33:369-375).

[22] The estimated C_{max} of the racemate was obtained by multiplying "C_{max} after a single dose" by "the accumulation factor calculated from $t_{1/2}$." The estimated C_{max} of esflurbiprofen was obtained by multiplying the estimated C_{max} of the racemate by 1/2. The estimated $AUC_{0\text{-}24h}$ of the racemate was obtained by multiplying "$AUC_{0\text{-}\infty}$ after a single dose" by 2 (the number of doses per day). The estimated $AUC_{0\text{-}24h}$ of esflurbiprofen was obtained by multiplying the estimated $AUC_{0\text{-}24h}$ of the racemate by 1/2, based on a report on administration of oral FP (Knadler MP et al. *Br J Clin Pharmacol.* 1992;33:369-375).

systemic exposure to unchanged compound following administration of the approved FP product at the recommended daily clinical dose. However, since the maximum daily dose studied in clinical studies was 80 mg, no information is available on the safety of ≥3 esflurbiprofen plasters applied per day (≥120 mg/day).

Thus, the proposed dosage and administration include a precautionary statement, "Do not apply more than 2 plasters per day." The package insert and other information materials for Loqoa Tape will include this statement in order to caution healthcare professionals and patients against using more than 2 plasters per day, in a manner similar to the package inserts for the approved oral FP and intravenous FP-ax. Given the use status of the approved NSAID patches (Mizutani H et al. *Journal of clinical therapeutics & medicines*. 2010;26:227-240, Mizutani H et al. *Journal of clinical therapeutics & medicines*. 2010;26:727-741), patients may use more than 2 plasters of esflurbiprofen simultaneously, depending on the number of affected sites, as with patients using the approved NSAIDs plasters. The applicant will therefore issue an alert regarding the proper use of esflurbiprofen plaster in order to ensure that patients do not apply more than 2 plasters at the same time.

PMDA's view:
Esflurbiprofen plaster has better dermal absorbability and systemic distribution than the approved FP patch formulations; this suggests that the impact of systemic drug exposure on the safety may differ between esflurbiprofen plaster and the approved FP patches. Further, data have suggested that the systemic exposure following application of 2 plasters of 40 mg esflurbiprofen was comparable to the systemic exposure following administration of oral FP or intravenous FP-ax. This suggests that esflurbiprofen plaster and the approved oral FP and intravenous FP-ax may have similar safety risks.

4.(ii).B.(2) Effect of esflurbiprofen plaster on QT interval
The applicant's explanation about the effect of esflurbiprofen plaster on QT interval:
Although no thorough QT/QTc studies were conducted, esflurbiprofen is unlikely to affect QT interval, for the following reasons:

- In an *in vitro* study, esflurbiprofen had no effect on hERG current. In dogs given a single intravenous dose of esflurbiprofen (10 mg/kg), no abnormal findings were observed in blood pressure, heart rate, or electrocardiogram. The esflurbiprofen exposure (C_{max}) in the dogs was approximately 66 times the C_{max} in humans receiving SFPP-3 (80 mg). Thus, the nonclinical study results do not raise any concerns about the safety in the cardiovascular system.

- Following repeated application of SFPP-3 (80 mg) in a high-dose safety study, no clinically significant findings, changes in blood pressure or heart rate, or prolongation of QT/QTc intervals were observed. C_{max} observed in this study exceeded the exposure to unchanged compound following administration of oral FP or intravenous FP-ax.

- Proarrhythmic effects have not been reported with the approved FP products either in the post-marketing safety reports or in the published literature.

PMDA's view:
Esflurbiprofen is unlikely to affect QT intervals, based on the clinical experience of FP products and the following findings: (a) C_{max} of unchanged esflurbiprofen in plasma following application of esflurbiprofen is unlikely to exceed the estimated concentration of unchanged FP following administration of intravenous FP-ax. (b) No adverse events related to proarrhythmic risk were observed in the clinical studies of esflurbiprofen.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

The applicant submitted the efficacy and safety evaluation data (i.e., the results from studies including the following): Japanese phase I studies in healthy adults (Study 2119-01-600 [5.3.3.1-02], Study 2119-02-601 [5.3.3.1-03], Study 2119-03-602 [5.3.3.1-04], Study 2119-04-602 [5.3.3.1-05], Study SFPP-01-CP01 [5.3.3.1-06]), phase II studies in patients with knee OA (Study 2119-06-641 [5.3.5.1-01, (Study 641)], Study SFPP-02-OA02 [5.3.5.1-02, (Study 02-OA02)], Study SFPP-02-OA03 [5.3.5.1-03, (Study

02-OA03)]), a phase III study (Study SFPP-03-OA01 [5.3.5.1-04, (study 03-OA01)]), and a long-term study in patients with OA (Study SFPP-03-OA02 [5.3.5.2-01, (long-term study)]).

In the following sections, "esflurbiprofen" refers to esflurbiprofen plaster (including the formulations for clinical studies). The doses shown are those of esflurbiprofen. Mentha oil is contained in the vehicle of Loqoa Tape.

4.(iii).A.(1) Phase I studies

4.(iii).A.(1).1) Skin safety study (5.3.3.1-02, Study 2119-01-600 [[redacted]])

A simple patch test and a photo-patch test were conducted to investigate the skin irritation and photosensitivity in healthy adult men (target sample size, 30) in a single-blinded condition in 1 study site in Japan.

Plasters containing esflurbiprofen (5, 10, or 20 mg), the base, or ketoprofen, or adhesive plasters were cut into 0.28 cm^2 pieces and applied, in a randomized manner, to the left and right paraspinal areas of each subject (6 patches per subject).

In the simple patch test, plasters were removed after a 48-hour application, and 30 minutes and 24 hours later, skin conditions were evaluated. No subjects had skin reactions to any test formulations either at 30 minutes or 24 hours after removal of plasters, showing a skin irritation index[23] of 0.

In the photo-patch test, plasters were removed after a 24-hour application and, 30 minutes later, followed by a 6-minute UV-A irradiation. At 30 minutes after irradiation, the skin was evaluated for light-induced urticaria and then shielded from light. Skin symptoms and photosensitivity reactions were evaluated at 24 and 47.5 hours after irradiation. No subjects had light-induced urticaria associated with any test formulations at 30 minutes after irradiation. No subjects had photosensitivity reactions to any test formulations either at 24 or 47.5 hours after irradiation.

Adverse events occurred in 60.0% (18 of 30 subjects). The main adverse event (events reported by ≥2 subjects) was erythema (46.7% [14 of 30 subjects] at the side of simple patch test, 56.7% [17 of 30 subjects] at the side of photo-patch test). Deaths, serious adverse events, or adverse events leading to discontinuation were not observed.

4.(iii).A.(1).2) Single application study (5.3.3.1-03, Study 2119-02-601 [[redacted]])

A placebo-controlled, randomized, single-blind, comparative study was conducted in healthy adult men (target sample size, 30 [10 subjects per group]) to investigate the safety, etc., of a single application of esflurbiprofen plaster in 1 study site in Japan.

The study consisted of 6 steps: Step 1, esflurbiprofen 2 mg or placebo (vehicle); Step 2, esflurbiprofen 5 mg or placebo; Step 3, esflurbiprofen 10 mg or placebo; Step 4, esflurbiprofen 20 mg or placebo; Step 5, esflurbiprofen 40 mg (2 plasters of 20 mg) or placebo; and Step 6, esflurbiprofen 60 mg (3 plasters of 20 mg) or placebo. The subjects were divided into 3 groups. Subjects in Group 1 participated in Steps 1 and 2; those in Group 2 participated in Steps 3 and 4; and those in Group 3 participated in Steps 5 and 6. In each step, the study drug was applied to the back of subjects for 24 hours as a single dose.

All 32 subjects who received the study drug were included in the safety analysis set. Four subjects discontinued the study.

Adverse events occurred in 29% (2 of 7 subjects) in the 2 mg group, 43% (3 of 7 subjects) in the 5 mg group, 14% (1 of 7 subjects) in the 10 mg group, 50% (3 of 6 subjects) in the 20 mg group, 57% (4 of 7 subjects) in the 40 mg group, 86% (6 of 7 subjects) in the 60 mg group, and 41% (7 of 17 subjects) in the vehicle group. Adverse events reported by ≥2 subjects in any group were application site erythema (14% [1 of 7 subjects] in the 2 mg group, 29% [2 of 7 subjects] in the 5 mg group, 14% [1 of 7 subjects] in the 10 mg group, 33% [2 of 6 subjects] in the 20 mg group, 57% [4 of 7 subjects] in the 40 mg group, 71% [5 of 7 subjects] in the 60 mg group, 41% [7 of 17 subjects] in the vehicle group), and application

[23] Skin irritation index = (sum of the highest score at each evaluation time point)/(number of subjects analyzed) × 100

site pruritus (12% [2 of 17 subjects] in the vehicle group). Deaths, serious adverse events, or adverse events leading to discontinuation were not observed.

Adverse events for which a causal relationship to the study drug could not be ruled out (adverse reactions) were observed in 29% (2 of 7 subjects) in the 2 mg group, 43% (3 of 7 subjects) in the 5 mg group, 14% (1 of 7 subjects) in 10 the mg group, 33% (2 of 6 subjects) in the 20 mg group, 57% (4 of 7 subjects) in the 40 mg group, 86% (6 of 7 subjects) in the 60 mg group, and 41% (7 of 17 subjects) in the vehicle group.

4.(iii).A.(1).3) Repeated application study (a) (5.3.3.1-04, Study 2119-03-602 [to])

A placebo-controlled, randomized, single-blind, comparative study was conducted in healthy adult men to investigate the safety, etc., of esflurbiprofen in 1 study site in Japan (target sample size, 20 [7 subjects in the esflurbiprofen 20 mg group, 7 subjects in the 40 mg group, 6 subjects in the vehicle group]).

A plaster of 20 mg esflurbiprofen, 2 plasters of 20 mg esflurbiprofen (i.e., 40 mg), or placebo (vehicle plaster) plaster were applied to the lower back of subjects once daily for 7 days.

All 20 subjects who received the study drug (7 in the 20 mg group, 7 in the 40 mg group, and 6 in the vehicle group) were included in the safety analysis set.

Adverse events occurred in 86% (6 of 7 subjects) in the 20 mg group, 100% (7 of 7 subjects) in the 40 mg group, and 100% (6 of 6 subjects) in the vehicle group. Adverse events reported by ≥2 subjects in any group were application site erythema (57% [4 of 7 subjects] in the 20 mg group, 71% [5 of 7 subjects] in the 40 mg group, 100% [6 of 6 subjects] in the vehicle group), application site pruritus (14% [1 of 7 subjects] in the 20 mg group, 14% [1 of 7 subjects] in the 40 mg group, 33% [2 of 6 subjects] in the vehicle group), application site dryness (43% [3 of 7 subjects] in the 20 mg group, 67% [4 of 6 subjects] in the vehicle group), occult blood positive (14% [1 of 7 subjects] in the 20 mg group, 14% [1 of 7 subjects] in the 40 mg group, 50% [3 of 6 subjects] in the vehicle group), haemoglobin decreased (29% [2 of 7 subjects] in the 40 mg group), white blood cell count increased (29% [2 of 7 subjects] in the 40 mg group), and application site oedema (33% [2 of 6 subjects] in the vehicle group). Deaths, serious adverse events, or adverse events leading to discontinuation were not observed.

Adverse drug reactions occurred in 86% (6 of 7 subjects) in the 20 mg group, 100% (7 of 7 subjects) in the 40 mg group, and 100% (6 of 6 subjects) in the vehicle group.

4.(iii).A.(1).4) Repeated application study (b) (5.3.3.1-05, Study 2119-04-602 [to])

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Esflurbiprofen 40 mg (2 plasters of 20 mg formulation) was administered to the lower back of subjects once daily for 7 days.

All 12 subjects who received the study drug (6 subjects in the 40 mg group, 6 subjects in the vehicle group) were included in the safety analysis set.

Adverse events occurred in 67% (4 of 6 subjects) in the 40 mg group and 100% (6 of 6 subjects) in the vehicle group. Adverse events reported by ≥2 subjects in any group were application site erythema (67% [4 of 6 subjects] in the 40 mg group, 67% [4 of 6 subjects] in the vehicle group), application site pruritus (17% [1 of 6 subjects] in the 40 mg group, 33% [2 of 6 subjects] in the vehicle group), application site reaction (33% [2 of 6 subjects] in the vehicle group), and application site discolouration (33% [2 of 6 subjects] in the vehicle group). Deaths, serious adverse events, or adverse events leading to discontinuation were not observed.

Adverse drug reactions occurred in 67% (4 of 6 subjects) in the 40 mg group and 100% (6 of 6 subjects) in the vehicle group.

4.(iii).A.(1).5) High dose safety study (5.3.3.1-06, Study SFPP-01-CP01 [[redacted] to [redacted]])

A placebo-controlled, randomized, single-blind, comparative study was conducted in healthy adult men (target sample size, 14 [7 subjects per group]) to investigate the safety, etc., of esflurbiprofen in a single study site in Japan.

The study consisted of a single application period and a repeated application period. Esflurbiprofen 80 mg (2 plasters of 40 mg) or placebo (vehicle plaster) was applied to the lower back of subjects as a single dose for 24 hours and then once daily for 7 consecutive days. Throughout the single and repeated application periods, subjects remained on the same study drug.

All 14 subjects who received the study drug in the single application period (7 in the 80 mg group, 7 in the vehicle group) were included in the safety analysis set for the single application period. Of the 14 subjects, 13 (6 in the 80 mg group, 7 in the vehicle group) were included in the safety analysis set for the repeated application period. (The remaining 1 subject [in the 80 mg group] was excluded because the subject had discontinued the study for personal reasons before the repeated application period.)

Adverse events occurred in 57% (4 of 7 subjects) in the 80 mg group and 43% (3 of 7 subjects) in the vehicle group during the single application period, and in 83% (5 of 6 subjects) in the 80 mg group and 71% (5 of 7 subjects) in the vehicle group during the repeated application period. Adverse events reported by ≥2 subjects in either group were application site erythema (43% [3 of 7 subjects] in the 80 mg group, 14% [1 of 7 subjects] in the vehicle group during the single application period; 50% [3 of 6 subjects] in the 80 mg group, 71% [5 of 7 subjects] in the vehicle group during the repeated application period), occult blood positive (14% [1 of 7 subjects] in the 80 mg group during the single application period; 50% [3 of 6 subjects] in the 80 mg group, 14% [1 of 7 subjects] in the vehicle group during the repeated application period), and alanine aminotransferase increased (14% [1 of 7 subjects] in the vehicle group during the single application period; 29% [2 of 7 subjects] in the vehicle group during the repeated application period). Deaths, serious adverse events, or adverse events leading to discontinuation were not observed.

Adverse drug reactions occurred in 57% (4 of 7 subjects) in the 80 mg group and 29% (2 of 7 subjects) in the vehicle group during the single application period and in 71% (5 of 7 subjects) in the 80 mg group and 83% (5 of 6 subjects) in the vehicle group during the repeated application period.

4.(iii).A.(2) Japanese early phase II study (5.3.5.1-01, Study 2119-06-641 [[redacted] to [redacted]])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in patients with knee OA (target sample size, 240 [60 subjects per group]) to investigate the efficacy and safety of esflurbiprofen in 27 study sites in Japan.

An esflurbiprofen plaster (5, 10, or 20 mg) or placebo (vehicle plaster) was applied once daily for 2 consecutive weeks.

Of 256 subjects who received the study drug, 248 (63 in the 5 mg group, 62 in the 10 mg group, 60 in the 20 mg group, 63 in the vehicle group) were included in the full analysis set (FAS) and the safety analysis set. The remaining 8 subjects (all registered in the same hospital) were excluded because their source data, including medical records, were unavailable because of the closure of the hospital. Of the 248 subjects, 236 (60 in the 5 mg group, 60 in the 10 mg group, 57 in the 20 mg group, 59 in the vehicle group) were included in the per protocol set (PPS) and in the efficacy analysis set. The remaining 12 subjects were excluded: 4 subjects with protocol deviations (1 subject in each group); and 9 subjects with the application period of ≤10 days (i.e., <75% of the predetermined 14-day period) (3 in the 5 mg group, 1 in the 10 mg group, 2 in the 20 mg group, 3 in the vehicle group, including duplicates). The percentage of subjects who discontinued the study was 4.8% (3 of 63 subjects) in the 5 mg group, 1.6% (1 of 62 subjects) in the 10 mg group, 3.3% (2 of 60 subjects) in the 20 mg group, and 4.8% (3 of 63 subjects) in the vehicle group.

Table 7 shows the percent change in the clinical symptom score[24] from baseline to 2 weeks after administration (the primary efficacy endpoint). No statistically significant difference was observed between the esflurbiprofen and placebo groups.

Table 7. Percent change in clinical symptom score from baseline to the last assessment (PPS, LOCF)

	Esflurbiprofen 5 mg	Esflurbiprofen 10 mg	Esflurbiprofen 20 mg	Vehicle
Baseline	12.7 ± 3.4 (60)	12.9 ± 3.9 (60)	12.9 ± 3.7 (57)	13.2 ± 3.7 (59)
Last assessment	7.6 ± 4.5 (60)	7.2 ± 4.5 (60)	6.4 ± 4.1 (57)	7.7 ± 4.6 (59)
Percent change	−40.9 ± 31.1 (60)	−45.3 ± 28.1 (60)	−51.7 ± 26.2 (57)	−42.0 ± 30.3 (59)
Comparison with overall esflurbiprofen group [a)]	*P* = 0.035			

Mean ± SD (number of subjects)
a) Jonckheere test (trend test, one-sided significance level of 0.025)

Table 8 shows the percent change in the visual analogue scale (VAS) of pain (when standing up from a chair) from baseline to the last assessment (the secondary endpoint).

Table 8. Percent change in VAS (mm; pain when standing up from a chair) from baseline to the last assessment (PPS)

	Esflurbiprofen 5 mg	Esflurbiprofen 10 mg	Esflurbiprofen 20 mg	Vehicle
Baseline	43.7 ± 19.9 (60)	48.1 ± 18.5 (60)	45.3 ± 19.7 (56)	45.8 ± 19.5 (59)
Last assessment	26.3 ± 21.6 (60)	24.7 ± 18.2 (60)	20.3 ± 18.2 (56)	28.5 ± 21.6 (59)
Percent change (%)	−38.4 ± 46.3 (60)	−49.6 ± 30.7 (60)	−57.7 ± 31.1 (56)	−38.3 ± 44.0 (59)
Comparison with overall esflurbiprofen group[a)]	*P* = 0.004			
Comparison with each esflurbiprofen group[b), c)]	-	*P* = 0.125	*P* = 0.006	

Mean ± SD (number of subjects)
a) Jonckheere test (trend test, one-sided significance level of 0.025)
b) Wilcoxon rank sum test (one-sided significance level of 0.025)
c) Multiplicity was adjusted by the fixed sequence procedure consisting of a comparison (1) between the overall esflurbiprofen group and the vehicle group, (2) between the vehicle and esflurbiprofen 20 groups, (3) between the vehicle and esflurbiprofen 10 groups, and (4) between the vehicle and esflurbiprofen 5 mg groups. (The primary endpoint was not included in the multiplicity adjustment).

Adverse events occurred in 20.6% (13 of 63 subjects) in the esflurbiprofen 5 mg group, 29.0% (18 of 62 subjects) in the 10 mg group, 21.7% (13 of 60 subjects) in the 20 mg group, and 33.3% (21 of 63 subjects) in the vehicle group. The main adverse events are shown in Table 9. No death occurred. A serious adverse event (ankle fracture) occurred in 1 subject (1.6%) in the esflurbiprofen 5 mg group, but its causal relationship to the study drug was ruled out and the outcome was reported as improved. Adverse events leading to discontinuation occurred in 4.8% in the esflurbiprofen 5 mg group (3 of 63 subjects; application site dermatitis, dizziness, and ankle fracture [1 subject each]), 3.3% in the 20 mg group (2 of 60 subjects; application site dermatitis [2 subjects]), and 4.8% in the vehicle group (3 of 63 subjects; neck pain, application site dermatitis, and application site erythema/application site pruritus [1 subject each]); the outcome of these events was reported as resolved, recovered, or improved.

Adverse drug reactions occurred in 11.1% (7 of 63 subjects) in the esflurbiprofen 5 mg group, 12.9% (8 of 62 subjects) in the 10 mg group, 15.0% (9 of 60 subjects) in the 20 mg group, and 12.7% (8 of 63 subjects) in the vehicle group.

[24] The sum of individual scores for the following parameters rated on a 4-point scale (0 [none], 1 [mild], 2 [moderate], and 3 [severe]): Pain symptoms (passive movement pain, pain on walking up and down the stairs, pain at rest, pain on pressure), inflammatory symptoms (swelling of soft tissue of knee joint, floating patella), and interference with activities of daily living (squatting, standing up, walking).

Table 9. Adverse events with an incidence of ≥2% in any group (safety analysis set)

	Esflurbiprofen 5 mg (N = 63)	Esflurbiprofen 10 mg (N = 62)	Esflurbiprofen 20 mg (N = 60)	Vehicle (N = 63)
Application site dermatitis	2 (3.2)	3 (4.8)	5 (8.3)	2 (3.2)
Blood urea increased	0	1 (1.6)	2 (3.3)	0
Pruritus	0	1 (1.6)	2 (3.3)	0
Dermatitis contact	0	0	2 (3.3)	3 (4.8)
Nasopharyngitis	1 (1.6)	4 (6.5)	0	1 (1.6)
Application site pruritus	1 (1.6)	2 (3.2)	0	1 (1.6)
Blood urine present	0	2 (3.2)	0	1 (1.6)
Upper respiratory tract inflammation	1 (1.6)	2 (3.2)	0	0
White blood cell count increased	0	1 (1.6)	0	3 (4.8)

n (%)

4.(iii).A.(3) Japanese late phase II study (a) (5.3.5.1-02, Study SFPP-02-OA02 [[redacted] to [redacted]])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in patients with knee OA[25] (target sample size, 400 [100 subjects per group]) to investigate the efficacy and safety of esflurbiprofen in 17 study sites in Japan.

An esflurbiprofen plaster (10, 20, or 40 mg) or placebo (vehicle plaster) was applied once daily for 2 consecutive weeks.

All 409 randomized subjects (102 in the 10 mg group, 103 in the 20 mg group, 102 in the 40 mg group, and 102 in the vehicle group) were included in the FAS, the safety analysis set, and the efficacy analysis set. The percentage of subjects who discontinued the study was 3.9% (4 of 102 subjects) in the 10 mg group, 4.9% (5 of 103 subjects) in the 20 mg group, 3.9% (4 of 102 subjects) in the 40 mg group, and 6.9% (7 of 102 subjects) in the vehicle group.

Table 10 shows the percent change in VAS (knee pain when standing up from a chair) from baseline to 2 weeks after the start of application, the primary efficacy endpoint. No statistically significant difference was observed in the paired comparison between the esflurbiprofen 40 mg and vehicle groups.

Table 10. Percent change in VAS (mm; knee pain when standing up from a chair) from baseline to the last assessment (FAS, LOCF)

	Esflurbiprofen 10 mg	Esflurbiprofen 20 mg	Esflurbiprofen 40 mg	Vehicle
Baseline	59.3 ± 14.9 (102)	60.1 ± 15.5 (103)	60.1 ± 13.7 (102)	60.1 ± 14.0 (102)
Last assessment	23.7 ± 20.5 (102)	27.6 ± 21.4 (103)	22.7 ± 19.0 (102)	24.7 ± 21.7 (102)
Percent change (%)	−60.9 ± 30.1 (102)	−55.0 ± 31.7 (103)	−62.8 ± 28.4 (102)	−59.7 ± 32.5 (102)
Difference from vehicle [95% CI] *P* value [a), b)]	−1.2 [−9.7, 7.2]	4.7 [−3.8, 13.1]	−3.2 [−11.6, 5.3] *P* = 0.287	

Mean ± SD (number of patients)

a) Wilcoxon rank sum test (one-sided significance level of 0.025)

b) Multiplicity was adjusted by the fixed sequence procedure consisting of a pairwise comparison (1) between the vehicle and esflurbiprofen 40 groups, (2) between the vehicle and esflurbiprofen 20 groups, and (3) between the vehicle and esflurbiprofen 10 mg groups.

Adverse events occurred in 25.5% (26 of 102 subjects) in the 10 mg group, 19.4% (20 of 103 subjects) in the 20 mg group, 26.5% (27 of 102 subjects) in the 40 mg group, and 26.5% (27 of 102 subjects) in the vehicle group. The main adverse events are shown in Table 11. Neither death nor serious adverse event was observed. Adverse events leading to discontinuation were observed in 2.9% in the 10 mg

[25] Main inclusion criteria: (a) X-ray examination of the evaluation knee joint within 90 days before the start of the observation period showed osteophyte formation in addition to narrowed joint space, osteosclerosis, or subchondral cyst; (b) NSAID therapy for knee osteoarthritis was continued for ≥4 weeks (28 days) before the beginning of the observation period; (c) a VAS of <80 mm for "knee pain when standing up from a chair" at the beginning of the observation period (for both knees in patients with bilateral knee OA); and (d) a VAS score of ≥40 mm for "knee pain when standing up from a chair" of the evaluation knee at the beginning of the application of the study drug and, as a result of discontinuation of NSAID therapy, a ≥15-mm worsening of VAS from the beginning of the observation period.

group (3 of 102 subjects; application site dermatitis, chest discomfort, and nausea/dizziness/palpitations [1 subject each]); 2.9% in the 20 mg group (3 of 103 subjects; application site dermatitis [3 subjects]); and 2.0% in the 40 mg group (2 of 102 subjects; application site dermatitis and stomach discomfort/vomiting [1 subject each]); and 6.9% in the vehicle group (7 of 102 subjects; application site dermatitis [2 subjects], application site erythema/application site pruritus, application site erythema, application site pruritus, eructation, and contusion [1 subject each]). The outcome was reported as resolved or recovered for all events.

Adverse drug reactions occurred in 16.7% (17 of 102 subjects) in the 10 mg group, 12.6% (13 of 103 subjects) in the 20 mg group, 21.6% (22 of 102 subjects) in the 40 mg group, and 19.6% (20 of 102 subjects) in the vehicle group.

Table 11. Adverse events with an incidence of ≥2% in any group (safety analysis set)

	Esflurbiprofen 10 mg (N = 102)	Esflurbiprofen 20 mg (N = 103)	Esflurbiprofen 40 mg (N = 102)	Vehicle (N = 102)
Application site erythema	8 (7.8)	7 (6.8)	9 (8.8)	11 (10.8)
Application site pruritus	1 (1.0)	1 (1.0)	2 (2.0)	3 (2.9)
Application site dermatitis	1 (1.0)	3 (2.9)	4 (3.9)	2 (2.0)
Blood urea increased	0	0	3 (2.9)	2 (2.0)
Blood urine present	0	0	1 (1.0)	2 (2.0)
Application site rash	5 (4.9)	4 (3.9)	3 (2.9)	1 (1.0)
Glucose urine present	3 (2.9)	0	1 (1.0)	1 (1.0)
Application site eczema	0	0	2 (2.0)	0
Stomach discomfort	0	0	2 (2.0)	0
Blood bilirubin increased	0	0	2 (2.0)	0

n (%)

4.(iii).A.(4) Japanese late phase II study (b) (5.3.5.1-03, Study SFPP-02-OA03 [[redacted] to [redacted]])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in patients with knee OA[26] (target sample size, 500 [125 subjects per group]) to investigate the efficacy and safety of esflurbiprofen in 59 study sites in Japan.

An esflurbiprofen plaster (10, 20, or 40 mg) or placebo (vehicle plaster) was applied once daily for 2 consecutive weeks.

All 509 randomized subjects (121 in the esflurbiprofen 10 mg group, 127 in the 20 mg group, 134 in the 40 mg group, and 127 in the vehicle group) were included in the FAS, the safety analysis set, and the efficacy analysis set. The percentage of subjects who discontinued the study was 0.8% (1 of 121 subjects) in the esflurbiprofen 10 mg group, 1.6% (2 of 127 subjects) in the 20 mg group, 3.7% (5 of 134 subjects) in the 40 mg group, and 2.4% (3 of 127 subjects) in the vehicle group.

Table 12 shows the change in VAS (knee pain when standing up from a chair) from baseline to 2 weeks after the start of application (the primary efficacy endpoint). A statistically significant difference was observed in the paired comparison between the esflurbiprofen 40 mg and vehicle groups.

[26] Main inclusion criteria: (a) In a standing weight-bearing X-ray of the evaluation knee during extension performed within 90 days before the beginning of the observation period, the evaluation knee was classified as Grade II or III by Kellgren-Lawrence classification, and the grade of the opposite knee did not exceed that of the evaluation knee; (b) NSAID therapy for knee osteoarthritis was continued for ≥3 weeks (21 days) before the beginning of the observation period and thereafter continued until the beginning of the withdrawal period; (c) a VAS score of <80 mm for "knee pain when standing up from a chair" of the evaluation knee at the beginning of the withdrawal period, a VAS score of ≥40 mm at the beginning of the application of the study drug, and as a result of discontinuation of NSAID therapy, a ≥15-mm worsening of VAS from the beginning of the observation period; (d) At the beginning of the application of the study drug, the score of the clinical symptoms (pain on walking up and down stairs) of the evaluation knee worsened by ≥1 point from the beginning of the withdrawal period; (e) The opposite knee was not treated with NSAIDs from 3 weeks (21 days) before the beginning of the observation period until the beginning of the withdrawal period, or the clinical symptom score (sum of pain symptom scores) of the opposite knee was ≤1 from the beginning of the observation period until the beginning of the application of the study drug; and (f) the clinical symptom score (sum of pain symptom scores) and the patient diary indicated that, throughout the observation period, the symptoms of the evaluation knee were worse than those of the opposite knee.

Table 12. Change in VAS (mm, knee pain when standing up from a chair) from baseline to the last assessment (FAS, LOCF)

	Esflurbiprofen 10 mg	Esflurbiprofen 20 mg	Esflurbiprofen 40 mg	Vehicle
Baseline	57.8 ± 12.3 (121)	56.0 ± 12.5 (127)	57.0 ± 12.4 (134)	58.4 ± 13.5 (126)
Last assessment	26.1 ± 17.5 (121)	24.5 ± 17.6 (127)	21.5 ± 16.7 (134)	28.4 ± 18.9 (126)
Change from baseline	−31.7 ± 17.1 (121)	−31.5 ± 16.1 (127)	−35.5 ± 17.1 (134)	−30.1 ± 18.8 (126)
Difference from vehicle [95% CI] [a)] *P* value [a), b)]	−1.9 [−6.0, 2.2]	−2.5 [−6.5, 1.5] *P* = 0.112	−6.1 [−10.1, −2.1] *P* = 0.001	

Mean ± SD (number of subjects)

a) Analysis of covariance (ANCOVA) model with baseline and treatment group as explanatory variables (one-sided significance level of 0.025)

b) Multiplicity was adjusted by the fixed sequence procedure consisting of a pairwise comparison (1) between the vehicle and esflurbiprofen 40 groups, (2) between the vehicle and esflurbiprofen 20 groups, and (3) between the vehicle and esflurbiprofen 10 mg groups.

Adverse events occurred in 15.7% (19 of 121 subjects) in the esflurbiprofen 10 mg group, 14.2% (18 of 127) in the 20 mg group, 17.2% (23 of 134) in the 40 mg group, and 14.2% (18 of 127) in the vehicle group. The main adverse events (adverse events with an incidence of ≥2% in any group) were application site dermatitis (6.6% [8 subjects] in the esflurbiprofen 10 mg group, 2.4% [3 subjects] in the 20 mg group, 7.5% [10 subjects] in the 40 mg group, 5.5% [7 subjects] in the vehicle group) and blood urea increased (1.7% [2 subjects] in the esflurbiprofen 10 mg group, 2.4% [3 subjects] in the 20 mg group, 2.2% [3 subjects] in the 40 mg group, 1.6% [2 subjects] in the vehicle group). No death occurred. A serious adverse event (vertigo) occurred in 1 of 134 subjects (0.7%) in the esflurbiprofen 40 mg group, but its causal relationship to the study drug was ruled out, and the outcome was reported as recovered. Adverse events leading to discontinuation were observed in 0.8% (1 of 121 subjects; application site dermatitis [1 subject]) in the esflurbiprofen 10 mg group, 0.8% (1 of 127 subjects; application site dermatitis [1 subject]) in the 20 mg group, 2.2% (3 of 134 subjects; application site dermatitis [3 subjects]) in the 40 mg group, and 1.6% (2 of 127 subjects; application site dermatitis, arthritis [1 subject each]) in the vehicle group. The outcome was reported as resolved or recovered in all subjects.

Adverse drug reactions occurred in 13.2% (16 of 121 subjects) in the esflurbiprofen 10 mg group, 7.9% (10 of 127 subjects) in the 20 mg group, 14.2% (19 of 134 subjects) in the 40 mg group, and 7.9% (10 of 127 subjects) in the vehicle group.

4.(iii).A.(5) Japanese phase III study (5.3.5.1-04, Study SFPP-03-OA01 [[redacted] to [redacted]])

An open-label,[27] randomized, parallel-group study was conducted in patients with knee OA[28] (target sample size, 620 [310 subjects per group]) to investigate the efficacy and safety of esflurbiprofen in 70 study sites in Japan. FP gel patch (Stayban pap 40 mg) was used as a control.

Subjects received dermal application of esflurbiprofen plaster (40 mg) once daily, or FP gel patch twice daily, to the pre-selected evaluation knee for 2 weeks.

All 633 randomized subjects (316 in the esflurbiprofen group, 317 in the FP group) were included in the FAS, the safety analysis set, and the efficacy analysis set. The percentage of subjects who discontinued

[27] This study was not a double-blind comparative trial, because the dosage regimen and properties of esflurbiprofen differ from those of the comparator, and because it was difficult to simultaneously apply both drugs to the evaluation knee of patients with knee OA, the target disease. The study was conducted in accordance with an operating manual containing detailed instructions, in order to ensure as much as possible that evaluators (subjects or investigators) are denied access to information that may help distinguish esflurbiprofen from the comparator, to minimize the chance of evaluators (subjects or investigators) to identify the study drug.

[28] Main inclusion criteria: (a) In a standing weight-bearing X-ray of the evaluation knee during extension performed within 90 days before the beginning of the observation period, the evaluation knee was classified as Grade II or III by Kellgren-Lawrence classification, and the grade of the opposite knee did not exceed that of the evaluation knee; (b) NSAID therapy for knee osteoarthritis was continued for ≥3 weeks (21 days) before the beginning of the observation period and thereafter continued until the beginning of the withdrawal period; (c) a VAS score of <80 mm for "knee pain when standing up from a chair" of the evaluation knee at the beginning of the withdrawal period, a VAS score of ≥40 mm at the beginning of the application of the study drug, and as a result of discontinuation of NSAID therapy, a ≥15-mm worsening of VAS from the beginning of the observation period; (d) At the beginning of the application of the study drug, the score of the clinical symptoms (pain on walking up and down stairs) of the evaluation knee worsened by ≥1 point from the beginning of the withdrawal period; (e) The opposite knee was not treated with analgesics including NSAIDs from 3 weeks (21 days) before the beginning of the observation period until the beginning of the withdrawal period, or the clinical symptom score (sum of pain symptom scores) of the opposite knee was ≤1 from the beginning of the observation period until the beginning of the application of the study drug; and (f) the clinical symptom score (sum of pain symptom scores) and the patient diary indicated that, throughout the observation period, the symptoms of the evaluation knee were worse than those of the opposite knee.

the study was 2.8% (9 of 316 subjects) in the esflurbiprofen group and 1.3% (4 of 317 subjects) in the FP group.

Table 13 shows the change in VAS (knee pain when standing up from a chair) from baseline to 2 weeks after the start of application, the primary efficacy endpoint. A statistically significant difference was observed in the paired comparison between the esflurbiprofen and FP groups, demonstrating the superiority of esflurbiprofen plaster to FP gel patch.

Table 13. Change from baseline in VAS (mm, knee pain when standing up from a chair) at the last assessment (FAS, LOCF)

	Esflurbiprofen[b)]	FP
Baseline	59.5 ± 12.7 (315)	59.3 ± 12.5 (317)
Last assessment	18.5 ± 15.3 (315)	28.8 ± 18.1 (317)
Change from baseline	−41.0 ± 15.5 (315)	−30.5 ± 15.9 (317)
Difference from FP [95% CI] [a)] *P* value [a)]	−10.4 [−12.7, −8.0] *P* < 0.001	

Mean ± SD (number of subjects)
a) ANCOVA model with baseline and treatment group as explanatory variables (one-sided significance level of 0.025)
b) One subject with missing data was excluded.

Adverse events occurred in 16.5% (52 of 316 subjects) in the esflurbiprofen group and 12.0% (38 of 317 subjects) in the FP group. The main adverse event (adverse event with an incidence of ≥2% in either group) was application site dermatitis (3.5% [11 of 316 subjects] in the esflurbiprofen group, 0.6% [2 of 317 subjects] in the FP group). No death occurred. Serious adverse events occurred in 0.6% (2 of 316 subjects; vertigo/skull fracture/subarachnoid haemorrhage, and melaena [1 subject each]) in the esflurbiprofen group and 0.3% (1 of 317 subjects; humerus fracture [1 subject]) in the FP group. A causal relationship to the study drug was ruled out for all of them except for vertigo. Adverse events leading to discontinuation were observed in 2.5% (8 of 316 subjects; application site dermatitis [3 subjects], rash, meniscus injury, melaena, spinal osteoarthritis, and vertigo [1 subject each]) in the esflurbiprofen group and 0.6% (2 of 317 subjects; application site dermatitis, and humerus fracture [1 subject each]) in the FP group. The outcome was reported as improved for humerus fracture and resolved or recovered for the rest.

Adverse drug reactions occurred in 13.0% (41 of 316 subjects) in the esflurbiprofen group and 3.8% (12 of 317 subjects) in the FP group.

4.(iii).A.(6) Long-term study (5.3.5.2-01, Study SFPP-03-OA02 [[redacted] to [redacted]])

An open-label, uncontrolled study was conducted in patients with OA (including non-knee OA)[29] (target sample size, 200 [100 subjects per group]) to investigate the safety and efficacy of esflurbiprofen in 11 study sites in Japan.

One plaster or 2 plasters (1 per evaluation site) of 40 mg esflurbiprofen were applied once daily for ≥36 weeks (up to 52 weeks whenever possible).

All 201 treated subjects (101 in the 40 mg group, 100 in the 80 mg group) were included in the FAS, the safety analysis set, and the efficacy analysis set. The percentage of subjects who discontinued the study was 17.8% (18 of 101 subjects) in the 40 mg group and 20.0% (20 of 100 subjects) in the 80 mg group. The evaluation sites are shown in Table 14.

[29] Main inclusion criteria: (a) Findings suggestive of degenerative changes in the evaluation site in an X-ray taken within 90 days before the start of the observation period, and (b) moderate or severe pain on motion, at rest, or on pressure at the evaluation site before application of the study drug, requiring long-term treatment with NSAIDs.

Table 14. Evaluation sites

	40 mg (101 subjects)	80 mg (100 subjects)	Total
Number of evaluation sites	101	200	301
Knee joint	46 (45.5)	146 (73.0)	192 (63.8)
Lumbar vertebrae	39 (38.6)	27 (13.5)	66 (21.9)
Cervical vertebrae	11 (10.9)	15 (7.5)	26 (8.6)
Shoulder joint	3 (3.0)	6 (3.0)	9 (3.0)
Elbow joint	1 (1.0)	2 (1.0)	3 (1.0)
Hip joint	0	2 (1.0)	2 (0.7)
Foot joint	0	1 (0.5)	1 (0.3)
Other	1 (1.0)	1 (0.5)	2 (0.7)

Number of sites (%)

The time course of clinical symptom score,[30] an efficacy endpoint, are shown in Table 15.

Table 15. Changes from baseline in clinical symptom score (FAS)

	Number of sites	Clinical symptom score	Change from baseline
Baseline	301	6.2 ± 2.1	
After 2 weeks	294	4.5 ± 2.2	−1.7 ± 1.8
After 12 weeks	289	3.1 ± 2.2	−3.1 ± 2.2
After 24 weeks	264	2.5 ± 1.9	−3.7 ± 2.2
After 36 weeks	249	2.3 ± 2.4	−3.8 ± 2.6
After 52 weeks	237	1.8 ± 2.0	−4.4 ± 2.3
At the end of treatment	301	2.2 ± 2.4	−4.0 ± 2.5

Mean ± SD

Adverse events occurred in 92.1% (93 of 101 subjects) in the 40 mg group and 95.0% (95 of 100 subjects) in the 80 mg group. The main adverse events are shown in Table 16. No death occurred. Serious adverse events occurred in 3.0% (3 of 101 subjects; gastric ulcer haemorrhage, breast cancer, vertigo positional [1 subject each]) in the 40 mg group and 5.0% (5 of 100 subjects; lower gastrointestinal haemorrhage, colon cancer, pubis fracture, lymphoma, pyelocystitis [1 subject each]) in the 80 mg group. A causal relationship to esflurbiprofen was ruled out for all of the above adverse events except for gastric ulcer haemorrhage. The outcome was reported as unchanged for pubis fracture and lymphoma and recovered or improved for all others. Adverse events leading to discontinuation were observed in 7.9% (8 of 101 subjects; application site dermatitis [4 subjects], ligament injury, breast cancer, gastric ulcer haemorrhage, and application site eczema [1 subject each]) in the 40 mg group and 7.0% (7 of 100 subjects; application site dermatitis [3 subjects], lower gastrointestinal haemorrhage, colon cancer, blood urea increased, and application site eczema [1 subject each]) in the 80 mg group. The outcome was reported as “improved” for ligament injury, breast cancer, and colon cancer, and “resolved or recovered” for the rest.

Adverse drug reactions occurred in 54.5% (55 of 101 subjects) in the 40 mg group and 52.0% (52 of 100 subjects) in the 80 mg group.

[30] The sum of individual scores for the following parameters rated on a 4-point scale (0 [none], 1 [mild], 2 [moderate], and 3 [severe]): Pain symptoms (pain on movement, pain at rest, pain on pressure), inflammatory symptoms (swelling, localized warmth), motion limitation, and interference with activities of daily living.

Table 16. Adverse events with an incidence of ≥2% in either group (safety analysis set)

	40 mg (N = 101)	80 mg (N = 100)
Nasopharyngitis	42 (41.6)	35 (35.0)
Application site dermatitis	34 (33.7)	27 (27.0)
Contusion	13 (12.9)	8 (8.0)
Application site eczema	12 (11.9)	11 (11.0)
Application site pruritus	9 (8.9)	1 (1.0)
Gastroenteritis	8 (7.9)	3 (3.0)
Abdominal discomfort	6 (5.9)	6 (6.0)
Back pain	6 (5.9)	6 (6.0)
Osteoarthritis	6 (5.9)	3 (3.0)
Application site erythema	5 (5.0)	7 (7.0)
Myalgia	5 (5.0)	0
Spinal osteoarthritis	5 (5.0)	3 (3.0)
Periarthritis	4 (4.0)	3 (3.0)
Diarrhoea	4 (4.0)	2 (2.0)
Tenosynovitis	4 (4.0)	0
Eczema	3 (3.0)	4 (4.0)
Ligament sprain	3 (3.0)	4 (4.0)
Musculoskeletal stiffness	3 (3.0)	3 (3.0)
Constipation	3 (3.0)	2 (2.0)
Stomatitis	3 (3.0)	2 (2.0)
Blood urine present	3 (3.0)	2 (2.0)
Influenza	3 (3.0)	1 (1.0)
Application site urticaria	3 (3.0)	0
Arthropod sting	3 (3.0)	0
Gastritis	2 (2.0)	5 (5.0)
Cystitis	2 (2.0)	3 (3.0)
Rhinitis allergic	2 (2.0)	3 (3.0)
Abdominal pain upper	2 (2.0)	2 (2.0)
Arthralgia	2 (2.0)	2 (2.0)
Musculoskeletal pain	2 (2.0)	2 (2.0)
Sciatica	2 (2.0)	2 (2.0)
Vertigo	2 (2.0)	1 (1.0)
Conjunctivitis	2 (2.0)	1 (1.0)
Conjunctivitis allergic	2 (2.0)	1 (1.0)
Synovial cyst	2 (2.0)	1 (1.0)
Seasonal allergy	2 (2.0)	1 (1.0)
Oedema peripheral	2 (2.0)	0
Gastroenteritis norovirus	2 (2.0)	0
Ligament injury	2 (2.0)	0
Bursitis	2 (2.0)	0
Trigger finger	2 (2.0)	0
Pollakiuria	2 (2.0)	0
Wound	1 (1.0)	4 (4.0)
Blood urea increased	1 (1.0)	3 (3.0)
Rib fracture	1 (1.0)	2 (2.0)
Blood creatinine increased	1 (1.0)	2 (2.0)
Haemorrhage subcutaneous	1 (1.0)	2 (2.0)
Periodontitis	0	3 (3.0)
Palpitations	0	2 (2.0)
Dyspepsia	0	2 (2.0)
Gastrooesophageal reflux disease	0	2 (2.0)
Polyp	0	2 (2.0)
Bronchitis	0	2 (2.0)
Pyelonephritis	0	2 (2.0)
Blood potassium increased	0	2 (2.0)
Protein urine present	0	2 (2.0)
Intervertebral disc disorder	0	2 (2.0)
Cervicobrachial syndrome	0	2 (2.0)
Hypoaesthesia	0	2 (2.0)
Ingrowing nail	0	2 (2.0)

n (%)

4.(iii).B Outline of the review by PMDA

4.(iii).B.(1) Efficacy

The applicant's explanation about the design of the Japanese phase III study (Study 03-OA01):
The chief complaint of patients with knee OA is pain, and 70% to 80% of patients complain about pain while walking, after a long walk, when walking up and down the stairs, and when standing up, and report interference with activities of daily living (Iwaya T. *Guidebook for the conservative management of knee osteoarthritis* [in Japanese]. 1st edition, 2001). The chief complaints of patients with knee OA are "pain with weight-bearing" and "pain on first movement." The primary efficacy endpoint was "knee pain when standing up from a chair" because this parameter measures "pain with weight-bearing" with good repeatability. The secondary endpoint was "knee pain while walking" because this is the most typical pain reported by 60% of patients with early-stage knee OA and by 80% of those with mid-stage knee OA. (Koshino T. *Manual for knee diagnosis* [in Japanese]. 5th edition, 2001). Each pain was assessed using VAS to allow quantitative assessment of symptoms reported by patients.

In the Japanese late phase II study in patients with knee OA (a) (Study 02-OA02), the dose-response relationship of esflurbiprofen was investigated in 4 treatment groups: the esflurbiprofen 10, 20, and 40 mg groups and the vehicle group. No clear dose-response relationship was observed in the percent change in VAS (knee pain when standing up from a chair), the primary endpoint, with only a small difference between the esflurbiprofen and vehicle groups. An exploratory post-hoc analysis was conducted to determine the percent change in VAS (knee pain when standing up from a chair) in the subgroup of patients with unilateral or unilateral-dominant knee OA and in the subgroup of patients who showed worsened pain on walking up and down the stairs as assessed by the physician. As shown in Table 17, the efficacy of esflurbiprofen 40 mg was suggested by a paired comparison between the vehicle and esflurbiprofen 40 mg groups. The applicant considered that this result may have been due to the following reasons: (a) In patients with bilateral knee OA, the symptoms of the opposite knee (the knee not evaluated) may have affected the efficacy evaluation in the evaluation knee. (b) Some patients had no worsening of physician-assessed pain (when walking up and down the stairs) despite worsening of patient-assessed VAS (knee pain when standing up from a chair) measured after NSAIDs discontinuation during the observation period. In these patients, the efficacy of esflurbiprofen may have not been evaluated accurately.

In order to minimize the bias in efficacy evaluation, the Japanese late phase II study (b) (Study 02-OA03) enrolled patients with unilateral knee OA, patients with unilateral-dominant knee OA (among those with bilateral knee OA), and patients with worsening of both (a) physician-assessed pain and (b) subject-assessed pain measured during the observation period. They were assigned to 4 treatment groups (esflurbiprofen 10, 20, 40 mg, or vehicle) to investigate the dose-response relationship of esflurbiprofen.[31] As a result, a dose-response relationship was observed in the change in VAS (knee pain when standing up from a chair), the primary efficacy endpoint, with a statistically significant difference in the paired comparison between the esflurbiprofen 40 mg and vehicle groups [see "4.(iii).A.(4) Japanese late phase II study (b)"]. Therefore, the Japanese phase III study (Study 03-OA01) used esflurbiprofen 40 mg and the same inclusion criteria used in the Japanese late phase II study (b) (Study 02-OA03).

[31] The following inclusion criteria were added: (a) A standing weight-bearing X-ray of the evaluation knee during extension taken within 90 days before the start of the observation period showed that the evaluation knee was in grade II or III by Kellgren-Lawrence classification and that the grade of the opposite knee did not exceed that of the evaluation knee; (b) the opposite knee was not treated with NSAIDs from 3 weeks (21 days) before the start of the observation period until the start of the withdrawal period, or the clinical symptom score (sum of pain symptom scores) of the opposite knee was ≤1 from the start of the observation period until the start of the application of the study drug; (c) the clinical symptom score (sum of pain symptom scores) and the patient diary indicated that, throughout the observation period, the symptoms of the evaluation knee were worse than those of the opposite knee; and (d) at the start of the application of the study drug, the score of the clinical symptoms (pain on walking up and down stairs) of the evaluation knee worsened by ≥1 point from the start of the withdrawal period.

Table 17. Difference between the esflurbiprofen and vehicle groups in the percent change of VAS (knee pain when standing up from a chair) from baseline in Japanese phase II study (a) (Study 02-OA02) (FAS)

	Esflurbiprofen 10 mg	Esflurbiprofen 20 mg	Esflurbiprofen 40 mg
Unilateral or unilateral dominant knee OA	−7.6 [−17.6, 3.4] (49)	−6.4 [−15.5, 2.7] (65)	−10.5 [−19.4, −1.8] (65)
Bilateral knee OA	3.1 [−5.8, 12.5] (68)	12.7 [3.7, 22.8] (66)	3.7 [−4.7, 12.9] (63)
With worsening of physician-assessed pain when walking up and down the stairs	−18.4 [−38.0, −2.8] (35)	−11.6 [−32.6, 4.6] (30)	−20.7 [−41.1, −4.6] (34)
Without worsening of physician-assessed pain when walking up and down the stairs	7.4 [−1.1, 17.0] (67)	12.4 [3.9, 22.9] (73)	6.6 [−1.7, 16.2] (68)

Hodes-Lehmann estimate of the median [95% CI] (number of subjects)

The Japanese phase III study (Study 03-OA01) used an approved FP gel patch as the comparator. According to the applicant, the double-dummy method was not used because it does not ensure blindness for the following reasons: (a) The dosage regimen and properties of the FP gel patch are different from those of esflurbiprofen plaster; (b) it is difficult to simultaneously apply both drugs to the evaluation knee of patients with knee OA, the target disease.

Therefore, the Japanese phase III study (Study 03-OA01) was not a double-blind comparative study. However, the following measures were taken to minimize the chance of evaluators (subjects or investigators) to identify the study drug:

(a) The appearance and weight of the package of both study drugs were identical so that the drugs could not be distinguished from each other before opening.
(b) An operating manual was prepared. It includes the following detailed instructions:
    (i) The study drug must be supplied to subjects directly by unblinded study collaborators, not by the investigators;
    (ii) Subjects must not be informed of the dosage regimen or properties of the drug used in the other treatment group; and
    (iii) The study drug must be removed from the knee before examinations by the investigators.

These measures were implemented to ensure as much as possible that evaluators (subjects or investigators) are denied access to information that may help distinguish esflurbiprofen from the comparator.

The applicant's explanation about the efficacy of esflurbiprofen:
In the Japanese late phase II study (a) (Study 02-OA03) and in the Japanese phase III study (Study 03-OA01), VAS (knee pain when standing up from a chair), the primary efficacy endpoint, differed statistically significantly between the esflurbiprofen 40 mg group and the vehicle or FP group (paired comparisons). The results of the secondary efficacy endpoints (Table 18) demonstrate that patient's assessments (VAS [knee pain while walking] and subject's impression) and physician's assessment (clinical symptoms and overall improvement) tended to be better in the esflurbiprofen 40 mg group than in the vehicle or FP group. Also, VAS (knee pain when standing up from a chair), the primary efficacy endpoint, showed an improving tendency as early as from 1 week after the beginning of treatment.

Table 18. Secondary efficacy endpoints in Japanese late phase II study (b) (Study 02-OA03) and Japanese phase III study (Study 03-OA01) (FAS)

	Japanese late phase II study (b) (Study 02-OA03)			Japanese phase III study (Study 03-OA01)		
	Esflurbiprofen 40 mg	Vehicle	Difference from vehicle [95% CI] [a)]	Esflurbiprofen 40 mg	FP	Difference from FP [95% CI] [a)]
VAS (knee pain when standing up from a chair) (1 week after application)	−30.7 ± 18.1 (130)	−25.5 ± 16.3 (126)	−5.7 [−9.6, −1.8]	−35.1 ± 15.6 (314)	−25.6 ± 14.9 (316)	−9.5 [−11.8, −7.2]
VAS (knee pain while walking) (2 weeks after application, LOCF)	−19.2 ± 17.3 (132)	−15.6 ± 16.9 (127)	−4.9 [−8.6, −1.2]	−25.1 ± 18.6 (315)	−16.2 ± 15.3 (317)	−7.8 [−10.0, −5.5]
Subject's impression (percentage of "much improved")	22.4% (30/134)	9.4% (12/127)	12.9 [4.2, 21.6]	31.3% (99/316)	12.0% (38/317)	19.3 [13.1, 25.6]
Overall improvement (percentage of "marked improvement")	29.1% (39/134)	14.2% (18/127)	14.9 [5.1, 24.7]	43.4% (137/316)	14.8% (47/317)	28.5 [21.8, 35.2]
Clinical symptoms	−6.4 ± 4.4 (134)	−5.3 ± 3.6 (127)	−1.2 [−2.0, −0.4]	−7.3 ± 3.5 (315)	−5.3 ± 3.5 (317)	−2.0 [−2.4, −1.5]

Mean ± SD (number of subjects)
a) ANCOVA model with baseline and treatment group as explanatory variables

Table 19 shows the time course of clinical symptoms[32] by site in the long-term study (Study SFPP-03-OA02). Clinical symptoms tended to improve within 52 weeks of treatment, with no clear difference in the degree of improvement among evaluation sites.

Table 19. Time course of clinical symptom score by evaluation site in long-term study (FAS)

	Knee joint			Lumbar vertebrae			Cervical vertebrae			Other [a)]		
	No. of sites	Score	Change	No. of sites	Score	Change	No. of sites	Score	Change	No. of sites	Score	Change
Baseline	192	6.6 ± 2.1	−	66	5.1 ± 1.4	−	26	5.8 ± 1.5	−	17	6.7 ± 2.8	−
After 2 weeks	189	4.7 ± 2.3	−1.8 ± 1.9	65	3.7 ± 1.9	−1.4 ± 1.4	24	4.9 ± 1.9	−1.0 ± 1.2	16	4.3 ± 2.4	−2.4 ± 2.6
After 12 weeks	189	3.4 ± 2.2	−3.2 ± 2.2	61	2.2 ± 1.8	−2.9 ± 1.8	25	3.7 ± 2.4	−2.1 ± 2.0	14	2.5 ± 2.2	−4.4 ± 3.5
After 24 weeks	173	2.7 ± 2.0	−3.8 ± 2.3	58	1.9 ± 1.6	−3.2 ± 1.6	22	2.3 ± 2.3	−3.5 ± 1.6	11	2.8 ± 2.1	−4.9 ± 3.4
After 36 weeks	164	2.6 ± 2.7	−3.9 ± 2.8	55	1.8 ± 1.5	−3.2 ± 1.8	20	1.8 ± 1.8	−3.8 ± 1.4	10	2.6 ± 2.0	−5.3 ± 2.9
After 52 weeks	154	1.9 ± 2.1	−4.6 ± 2.4	54	1.4 ± 1.5	−3.6 ± 1.8	19	1.4 ± 1.5	−4.1 ± 1.4	10	3.0 ± 2.2	−4.9 ± 3.5
At the end of the study	192	2.3 ± 2.6	−4.2 ± 2.6	66	1.6 ± 1.8	−3.5 ± 1.9	26	2.2 ± 2.4	−3.6 ± 2.1	17	2.5 ± 2.1	−4.2 ± 3.0

Mean ± SD, −: not applicable
a) Shoulder joint (9 sites), elbow joint (3 sites), hip joint (2 sites), foot joint (1 site), thoracic vertebrae (1 site), hallux joint (1 site), 17 in total

The applicant's conclusion:
The above data demonstrate the efficacy of esflurbiprofen in OA.

PMDA's view:
The Japanese phase III study (Study 03-OA01) in patients with knee OA demonstrated the superiority of esflurbiprofen 40 mg to FP gel patch, as assessed by VAS (knee pain when standing up from a chair), the primary efficacy endpoint. In the Japanese late phase II study (b) (Study 02-OA03), a paired comparison showed a statistically significant difference in efficacy between vehicle and esflurbiprofen 40 mg. Studies 03-OA01 and 02-OA03 showed that VAS (knee pain while walking) tended to be better in the esflurbiprofen 40 mg group than in the FP or vehicle group. These results demonstrate the efficacy of esflurbiprofen in knee OA. In addition, the active ingredient esflurbiprofen is the (*S*)-enantiomer of FP (the active component FP). FP has been used for many years as an anti-inflammatory analgesic agent for patients with OA [see "3.(i) Summary of pharmacology studies"]. Esflurbiprofen ((*S*)-enantiomer of FP) has a greater tissue distribution than approved FP patches [see "4.(ii) Summary of clinical pharmacology studies"]. These data suggest that esflurbiprofen is expected to be effective also for OA

[32] The sum of individual scores for the following parameters rated on a 4-point scale (0 [none], 1 [mild], 2 [moderate], and 3 [severe]): Pain symptoms (pain on movement, pain at rest, pain on pressure), inflammatory symptoms (swelling, localized warmth), motion limitation, and interference with activities of daily living.

in other joints than the knees. Mentha oil (36.2 mg) was contained in the vehicle used in the clinical studies; Study 02-OA03 confirmed the add-on effect of esflurbiprofen 40 mg to mentha oil.

4.(iii).B.(2) Safety

The applicant explained the safety of esflurbiprofen based on results from a pooled analysis and a long-term study in patients with OA. The pooled analysis used data from 4 studies: the Japanese phase II studies (Studies 641, 02-OA02 and 02-OA03) and the Japanese phase III study (Study 03-OA01), all conducted in patients with knee OA with for 2 weeks. (These studies are collectively referred to as "the 2-week OA studies").

The applicant's explanation:

The tables below show the incidence of adverse events in the 2-week OA studies (Table 20) and in the long-term study (Table 16) [see "4.(iii).A.(6) Long-term study"]. [redacted][33][redacted]. No death occurred in any of the studies. Serious adverse events occurred in 5 subjects (ankle fracture, vertigo, vertigo/skull fracture/subarachnoid haemorrhage, melaena, and humerus fracture [1 subject each]) in the 2-week OA studies and in 8 subjects (gastric ulcer haemorrhage, breast cancer, vertigo positional, lower gastrointestinal haemorrhage, colon cancer, pubis fracture, lymphoma, and pyelonephritis [1 subject each]) in the long-term study. The outcome was reported as recovered or improved. Adverse events at the application site (e.g., application site dermatitis) accounted for many of the "adverse events leading to discontinuation," both in the 2-week OA studies and in the long-term study.

In the 2-week OA studies, the incidence of adverse events tended to be higher with esflurbiprofen than with FP gel patch. This was mainly due to adverse events at the application site (9.4% [62 of 638 subjects] with esflurbiprofen ≤20 mg, 11.1% [61 of 552 subjects] with 40 mg, 1.6% [5 of 317 subjects] with FP gel patch, 9.9% [29 of 292 subjects] with vehicle) and gastrointestinal disorders (gastrointestinal disorders SOC) (1.7% [11 of 638 subjects] with esflurbiprofen ≤20 mg, 2.0% [11 of 552 subjects] with 40 mg, 0.9% [3 of 317 subjects] with FP gel patch, 1.4% [4 of 292 subjects] with vehicle). No clear dose-response relationship was observed in the incidence of adverse events reported in the subjects treated with esflurbiprofen.

In the long-term study, esflurbiprofen was administered to 201 subjects. Among these subjects, 81.2% (82 of 101 subjects) in the 40 mg group and 79.0% (79 of 100 subjects) in the 80 mg group were treated with esflurbiprofen for ≥52 weeks. The median duration of application [range] was 51.9 [4.9, 54.0] weeks for the 40 mg group and 51.9 [1.6, 54.0] weeks for the 80 mg group. Table 22 shows the incidence of adverse events at the application site and the non-application site by treatment duration in the long-term study. The incidence of adverse events at the application site was higher in the 4th to 8th weeks of application than in other periods, with approximately half of events occurring within 12 weeks of application. As for the non-application site adverse events, there was no tendency of any specific adverse events occurring in any specific period, either in the 40 or 80 mg group.

Subgroup analysis by age (<65 years and ≥65 years):

In the long-term study, the incidence of adverse events at the application site was 41.1% (46 of 112 sites) in subjects aged <65 years and 51.3% (97 of 189 sites) in subjects aged ≥65 years, showing a tendency of a higher incidence in the population aged ≥65 years. Since elderly patients have reduced physical function (e.g., reduced metabolism and excretion) and are thus more prone to adverse reactions, esflurbiprofen should be administered carefully to these population while closely monitoring their conditions.

[33] [redacted]

Table 20. Incidence of adverse events in the 2-week OA studies

	Vehicle (N = 292)	Esflurbiprofen ≤20 mg (N = 638)	Esflurbiprofen 40 mg (N = 552)	FP gel patch (N = 317)
Adverse events	66 (22.6)	127 (19.9)	102 (18.5)	38 (12.0)
Adverse events resulting in death	0	0	0	0
Serious adverse events	0	1	3	1
Adverse events leading to discontinuation	12	13	13	2
Adverse drug reactions	38 (13.0)	80 (12.5)	82 (14.9)	12 (3.8)
Adverse events with an incidence of ≥2% in any group				
Application site dermatitis	11 (3.8)	25 (3.9)	25 (4.5)	2 (0.6)
Application site erythema	12 (4.1)	17 (2.7)	15 (2.7)	0
Blood urea increased	4 (1.4)	8 (1.3)	11 (2.0)	3 (0.9)

n (%)

Table 21. Incidence of adverse events in Study SFPP-[redacted]-[redacted]01

	Esflurbiprofen 40 mg (N = 41)	FP patch (N = 41)
Adverse events	9 (22.0)	4 (9.8)
Adverse events resulting in death	0	0
Serious adverse events	0	0
Adverse events leading to discontinuation	2	0
Adverse drug reactions	7 (17.1)	3 (7.3)
Adverse events reported by ≥2 subjects in either group		
Application site pruritus	3 (7.3)	0

n (%)

Table 22. Incidence of adverse events by treatment duration in the long-term study

Treatment duration (weeks)			≤2	>2 and ≤4	>4 and ≤8	>8 and ≤12	>12 and ≤16	>16 and ≤20	>20 and ≤24
Adverse events at the application site	Application site	No. of sites	301	299	298	291	282	271	267
		No. of affected sites (%)	11 (3.7)	18 (6.0)	40 (13.4)	21 (7.2)	17 (6.0)	14 (5.2)	9 (3.4)
Adverse events at the non-application sites	Esflurbiprofen 40 mg	No. of patients	101	101	100	97	95	92	90
		No. of affected patients (%)	15 (14.9)	18 (17.8)	34 (34.0)	19 (19.6)	22 (23.2)	17 (18.5)	16 (17.8)
	Esflurbiprofen 80 mg	No. of patients	100	99	99	97	94	90	89
		No. of affected patients (%)	18 (18.0)	18 (18.2)	24 (24.2)	17 (17.5)	14 (14.9)	12 (13.3)	14 (15.7)
Treatment duration (weeks)			>24 and ≤28	>28 and ≤32	>32 and ≤36	>36 and ≤40	>40 and ≤44	>44 and ≤48	>48 and ≤52
Adverse events at the application site	Application site	No. of sites	258	250	250	249	245	245	238
		No. of affected sites (%)	20 (7.8)	9 (3.6)	10 (4.0)	5 (2.0)	6 (2.4)	3 (1.2)	1 (0.4)
Adverse events at the non-application sites	Esflurbiprofen 40 mg	No. of patients	90	85	85	84	84	84	82
		No. of affected patients (%)	18 (20.0)	12 (14.1)	11 (12.9)	9 (10.7)	11 (13.1)	10 (11.9)	5 (6.1)
	Esflurbiprofen 80 mg	No. of patients	84	83	83	83	81	81	79
		No. of affected patients (%)	13 (15.5)	12 (14.5)	15 (18.1)	15 (18.1)	11 (13.6)	12 (14.8)	6 (7.6)

4.(iii).B.(2).1) Gastrointestinal disorders

The applicant's explanation about adverse events related to gastrointestinal disorders:
NSAIDs are known to pose a risk of gastrointestinal disorders because they inhibit COX, thereby inhibiting the synthesis of PGs (which protect gastric mucosa and inhibit gastric acid secretion) and directly stimulating the gastric mucosal cells.

The incidence of gastrointestinal disorders (gastrointestinal disorders SOC) in the 2-week OA studies and the long-term study are shown in Tables 23 and 24. Many of the adverse events observed were mild in severity. Events of moderate severity were abdominal discomfort, vomiting, and lower gastrointestinal haemorrhage (in 1 subject each). Severe events were melaena and gastric ulcer

haemorrhage (in 1 subject each). Serious adverse events were melaena,[34] gastric ulcer haemorrhage,[35] and lower gastrointestinal haemorrhage[36] (in 1 subject each). The incidence of adverse events related to ulcers, etc.[37] of gastrointestinal organs was 0.3% (in 2 of 638 subjects) with esflurbiprofen ≤20 mg, 1.1% (in 6 of 552 subjects) with 40 mg, 0.3% (in 1 of 292 subjects) with vehicle, and 0% with FP gel patch in the 2-week OA studies; and 6.9% (in 7 of 101 subjects) in the esflurbiprofen 40 mg group and 9.0% (in 9 of 100 subjects) in the 80 mg group in the long-term study.

In the long-term study, the incidence rate of gastrointestinal disorders (events per patient-year) was 0.33 in the esflurbiprofen 40 mg group and 0.39 in the 80 mg group. There was no consistent tendency in the timing of onset of the adverse events related to gastrointestinal disorders observed in the long-term study. Thus, the incidence of gastrointestinal disorders did not tend to increase with increased duration of treatment.

In the 2-week OA studies, the incidence of gastrointestinal disorders tended to be higher in the esflurbiprofen 40 mg group than in the FP gel patch group. A total of 218 gastrointestinal adverse reactions occurred in 2405 subjects treated with an oral FP product (Froben Tab.40) before the approval of the drug (Interview Form of Froben Tab. 40 and Froben Gr. 8%, revised in May 2012), and 1.0% (13 of 1300) of subjects receiving an intravenous FP-ax product (Ropion Intravenous 50 mg) experienced gastrointestinal disorders before the approval of the drug (Interview Form of Ropion Intravenous 50 mg, revised in May 2012). Thus, the incidence of gastrointestinal disorders were not much higher in subjects receiving esflurbiprofen than in those receiving oral FP or intravenous FP-ax.

Table 23. Incidence of gastrointestinal disorders in the 2-week OA studies

	Vehicle (N = 292)	Esflurbiprofen ≤20 mg (N = 638)	Esflurbiprofen 40 mg (N = 552)	FP gel patch (N = 317)
Gastrointestinal disorders	4 (1.4)	11 (1.7)	11 (2.0)	3 (0.9)
Abdominal discomfort	0	1 (0.2)	4 (0.7)	0
Constipation	0	0	2 (0.4)	1 (0.3)
Diarrhoea	0	2 (0.3)	2 (0.4)	1 (0.3)
Stomatitis	1 (0.3)	2 (0.3)	0	1 (0.3)
Dyspepsia	0	1 (0.2)	1 (0.2)	0
Abdominal distension	0	1 (0.2)	0	0
Melaena	0	0	1 (0.2)	0
Vomiting	0	0	1 (0.2)	0
Epigastric discomfort	0	0	1 (0.2)	0
Abdominal pain	1 (0.3)	0	0	0
Enterocolitis	1 (0.3)	0	0	0
Eructation	1 (0.3)	0	0	0
Gastric ulcer	0	1 (0.2)	0	0
Gingival pain	0	1 (0.2)	0	0
Nausea	0	1 (0.2)	0	0
Toothache	0	1 (0.2)	0	0

n (%)

[34] The timing of onset suggested that the melaena was probably due to biopsy performed during endoscopy of the lower gastrointestinal tract at another hospital.

[35] The subject had also atrophic gastritis and was positive for *Helicobacter pylori*, but the event was determined to have causal relationship to esflurbiprofen.

[36] No clear mucosal disorder was observed on endoscopy of either the upper or lower gastrointestinal tract.

[37] Gastrointestinal perforation, ulceration, haemorrhage or obstruction (SMQ)

Table 24. Incidence of gastrointestinal disorders in the long-term study

	Esflurbiprofen 40 mg (N = 101)	Esflurbiprofen 80 mg (N = 100)
Gastrointestinal disorders	21 (20.8)	23 (23.0)
Abdominal discomfort	6 (5.9)	6 (6.0)
Abdominal pain	1 (1.0)	0
Abdominal pain upper	2 (2.0)	2 (2.0)
Constipation	3 (3.0)	2 (2.0)
Dental caries	1 (1.0)	1 (1.0)
Diarrhoea	4 (4.0)	2 (2.0)
Duodenal ulcer	0	1 (1.0)
Dyspepsia	0	2 (2.0)
Gastric ulcer	0	1 (1.0)
Gastric ulcer haemorrhage	1 (1.0)	0
Gastritis	2 (2.0)	5 (5.0)
Gastritis erosive	0	1 (1.0)
Gastrooesophageal reflux disease	0	2 (2.0)
Haemorrhoids	0	1 (1.0)
Nausea	1 (1.0)	0
Oesophagitis	1 (1.0)	0
Periodontal disease	1 (1.0)	0
Stomatitis	3 (3.0)	2 (2.0)
Toothache	1 (1.0)	0
Lower gastrointestinal haemorrhage	0	1 (1.0)

n (%)

PMDA's view:
In the 2-week OA studies, the incidence of gastrointestinal disorders was highest in the esflurbiprofen 40 mg group. In the long-term study, the incidence of gastrointestinal disorders tended to be higher in the 80 mg group than in the 40 mg group. Also, serious gastrointestinal disorders were observed in clinical studies. Therefore, attention should be paid to gastrointestinal disorders that may occur in patients treated with esflurbiprofen plaster. In addition, the incidence of gastrointestinal disorders tended to be higher in subjects treated with esflurbiprofen than in those treated with an approved FP gel patch, and the systemic exposure in subjects receiving esflurbiprofen 80 mg was comparable to the systemic exposure in those receiving oral FP or intravenous FP-ax, both of which are known to cause gastrointestinal disorders [see "4.(ii) Summary of clinical pharmacology studies"]. Therefore, esflurbiprofen may pose a safety risk comparable to that posed by the approved oral FP and intravenous FP-ax. Therefore, the applicant should issue an alert for gastrointestinal disorders that may occur in patients receiving esflurbiprofen, in a manner similar to the alert for patients receiving the approved oral FP or intravenous FP-ax. Patients with OA are expected to use esflurbiprofen for a long time and elderly patients are expected use esflurbiprofen. Therefore, the applicant should continue to investigate the occurrence of gastrointestinal disorders, etc. in routine clinical use, including long-term use, via post-marketing surveillance.

4.(iii).B.(2).2) Renal dysfunction

The applicant's explanation about renal dysfunction:
NSAIDs are known to pose a risk of affecting renal function because they inhibit COX, thereby inhibiting the synthesis of PGs, which affect Na resorption in the kidney. Oral and intravenous NSAIDs, including FP, are known to cause renal function-related adverse reactions (e.g., acute kidney injury, oliguria, and micturition frequency decreased) as well as laboratory abnormalities.

Tables 25 and 26 show the incidence of renal function-related adverse events[38] in the 2-week OA studies and in the long-term study. All the observed events were mild laboratory abnormalities, and no serious renal function-related adverse events occurred.

In the long-term study, estimated glomerular filtration rate (eGFR) decreased from baseline: the 40 mg group, 76.0 ± 15.0 mL/min/1.73 m^2 (baseline) to 73.2 ± 13.7 mL/min/1.73 m^2 (Week 52); the 80 mg group, 73.4 ± 17.5 mL/min/1.73 m^2 (baseline) to 70.6 ± 15.0 mL/min/1.73 m^2 (Week 44) and to 70.6 ±

[38] Acute renal failure (SMQ), chronic kidney disease (SMQ), and blood urine present (PT)

14.2 mL/min/1.73 m^2 (Week 52); these changes were small, suggesting that a 52-week application of esflurbiprofen are unlikely to pose major problems. eGFR decreased by ≥25% from baseline to Week 52 in 2 subjects: In one subject, eGFR showed a transient increase only immediately after application, but remained at a level similar to that at the start of the observation period. In the other subject, the decreased eGFR was probably due to pyelonephritis (occurring at Week 44) and, after therapeutic intervention, eGFR was improving at Week 48 and Week 52. Therefore, the subject was not followed up after Week 52. The event was not recovered as of Week 52.

In the clinical studies of esflurbiprofen, renal function-related adverse reactions consisted entirely of mild laboratory abnormalities, and there were no adverse events markedly different from the findings in patients treated with the approved NSAID patches.

In clinical studies conducted so far, no clinically significant renal function-related adverse events occurred in subjects treated with ≤2 plasters of esflurbiprofen. However, the systemic exposure in patients treated with esflurbiprofen 80 mg was similar to the systemic exposure in patients treated with oral FP or intravenous FP-ax [see "4.(ii) Summary of clinical pharmacology studies"]. Esflurbiprofen may thus pose a risk of renal dysfunction comparable to that posed by the approved oral FP and intravenous FP-ax. Therefore, attention should be paid to serious renal function-related adverse events, etc. that may occur in patients treated with esflurbiprofen plaster.

Table 25. Incidence of renal function-related adverse events in the 2-week OA studies

	Vehicle (N = 292)	Esflurbiprofen ≤20 mg (N = 638)	Esflurbiprofen 40 mg (N = 552)	FP gel patch (N = 317)
Renal function-related adverse events	11 (3.8)	14 (2.2)	15 (2.7)	7 (2.2)
Blood urea increased	4 (1.4)	8 (1.3)	11 (2.0)	3 (0.9)
Blood creatinine increased	1 (0.3)	1 (0.2)	6 (1.1)	0
Blood urine present	4 (1.4)	3 (0.5)	1 (0.2)	1 (0.3)
Protein urine present	1 (0.3)	1 (0.2)	1 (0.2)	2 (0.6)
Blood potassium increased	3 (1.0)	3 (0.5)	0	1 (0.3)

n (%)

Table 26. Incidence of renal function-related adverse events in the long-term study

	Esflurbiprofen 40 mg (N = 101)	Esflurbiprofen 80 mg (N = 100)
Renal function-related adverse events	4 (4.0)	8 (8.0)
Blood urine present	3 (3.0)	2 (2.0)
Blood urea increased	1 (1.0)	3 (3.0)
Blood creatinine increased	1 (1.0)	2 (2.0)
Blood potassium increased	0	2 (2.0)
Protein urine present	0	2 (2.0)

n (%)

PMDA's view:
Esflurbiprofen may have a risk of renal function-related adverse events comparable to that posed by the approved oral FP and intravenous FP-ax, for the following reasons: (a) Serious renal function-related adverse events have been reported with the approved oral and intravenous NSAIDs. (b) The systemic exposure in subjects receiving esflurbiprofen 80 mg plaster was similar to the systemic exposure in patients receiving oral FP or intravenous FP-ax [see "4.(ii) Summary of clinical pharmacology studies"]. Therefore, the applicant should issue an alert regarding the use of esflurbiprofen in patients with renal impairment, in a manner similar to the alert for patients receiving the approved oral FP or intravenous FP-ax. Also, since esflurbiprofen is expected to be used in patients with OA for a long period and also in elderly patients, the applicant should further investigate the occurrence of renal function-related adverse events in routine clinical use, including long-term use, via post-marketing surveillance.

4.(iii).B.(2).3) Cardiovascular disorders

The applicant's explanation about cardiovascular adverse events:

Cardiovascular adverse events are a risk associated with NSAID therapy (Bhala N et al, *Lancet.* 2013;382:769-779, Food and Drug Administration. *Drug Safety Communications.* July 9, 2015, European Medicines Agency. *Assessment report.* Oct 18, 2012, etc.).

Tables 27 and 28 show the incidence of cardiovascular adverse events[39] in the 2-week OA studies and in the long-term study. No severe or serious adverse events occurred. In the long-term study, heart rate increased observed in the 80 mg group was assessed as moderate in severity, whereas all the other adverse events were mild. In the 2-week OA studies, a causal relationship to esflurbiprofen was ruled out for all cardiovascular adverse events, except for the mild palpitations in 1 subject treated with esflurbiprofen ≤20 mg.

In the long-term study, the incidence of cardiovascular adverse events tended to be higher in subjects receiving concomitant NSAIDs (9.3% [4 subjects] in the esflurbiprofen 40 mg group, 9.3% [4 subjects] in the 80 mg group) than in subjects not receiving concomitant NSAIDs (0% in the 40 mg group, 1.8% [1 subject] in the 80 mg group). A causal relationship to esflurbiprofen was ruled out for all events.

Oedema (face and hands), as well as palpitations, have been reported with the approved NSAID patches. The following adverse reactions have been reported with oral and intravenous NSAIDs, including FP: arrhythmia, angina pectoris-like attacks, cardiac palpitation, blood pressure increased, and blood pressure decreased.

Esflurbiprofen may pose a risk of cardiovascular adverse events comparable to that posed by oral and intravenous NSAIDs including FP, for the following reasons: (a) Some evidence suggests that NSAIDs may dose-dependently increase the risk of cardiovascular adverse events; (b) the systemic exposure in subjects receiving 2 plasters of 40 mg esflurbiprofen was comparable to the systemic exposure in patients receiving oral FP or intravenous FP-ax [see "4.(ii) Summary of clinical pharmacology studies"]. Some reports have suggested that FP, the racemate of esflurbiprofen, has a risk of causing cardiovascular adverse events (Bavry AA et al. *Circ Cardiovasc Qual Outcomes.* 2014;7:603-610, Shau WY et al. *BMC Cardiovasc Diord.* 2012;12:4). However, there are no reports suggesting that FP has a greater risk of cardiovascular adverse events than other NSAIDs. The applicant will issue an alert regarding cardiovascular events that may occur in patients receiving esflurbiprofen, in a manner similar to the alert for patients receiving oral FP or intravenous FP-ax.

Table 27. Incidence of cardiovascular adverse events in the 2-week OA studies

	Vehicle (N = 292)	Esflurbiprofen ≤20 mg (N = 638)	Esflurbiprofen 40 mg (N = 552)	FP gel patch (N = 317)
Cardiovascular adverse events	0	1 (0.2)	1 (0.2)	1 (0.3)
Palpitations	0	1 (0.2)	1 (0.2)	0
Atrial fibrillation	0	0	0	1 (0.3)

n (%)

[39] Cardiac failure (SMQ), ischaemic heart disease (SMQ), cardiac arrhythmias (SMQ)

Table 28. Incidence of cardiovascular adverse events in the long-term study

	Esflurbiprofen 40 mg (N = 101)	Esflurbiprofen 80 mg (N = 100)
Cardiovascular adverse events	4 (4.0)	5 (5.0)
Palpitations	0	2 (2.0)
Oedema peripheral	2 (2.0)	0
Cardiac failure congestive	1 (1.0)	0
Extrasystoles	1 (1.0)	0
Myocardial ischaemia	1 (1.0)	0
Angina pectoris	0	1 (1.0)
Atrial fibrillation	0	1 (1.0)
Heart rate increased	0	1 (1.0)
Electrocardiogram Q wave abnormal	0	1 (1.0)

n (%)

PMDA's view:
The systemic exposure following application of esflurbiprofen 80 mg (2 plasters of 40 mg) is comparable to the systemic exposure following administration of oral FP or intravenous FP-ax [see "4.(ii) Summary of clinical pharmacology studies"]. This suggests that esflurbiprofen may pose a risk of cardiovascular adverse events comparable to that posed by the approved oral and intravenous NSAIDs including FP. However, no clinically significant events occurred in subjects treated with ≤2 esflurbiprofen plasters in clinical studies conducted so far. Further, FP has been used for a long time in clinical practice, but there are no data suggesting that FP has a higher risk of cardiovascular adverse events than other NSAIDs. Thus, at present, PMDA accepts the applicant's proposal to issue an alert for patients with cardiac dysfunction, in a manner similar to the alert for those using the approved oral FP or intravenous FP-ax. Since patients may use several plasters simultaneously, the applicant should issue cautionary statements regarding "the maximum number of plasters applied at a time" and "concomitant use of other NSAIDs. Esflurbiprofen is expected to be used for a long time in patients with OA and also in elderly patients with a higher risk of cardiovascular adverse events. Therefore, the applicant should further investigate the esflurbiprofen-associated risk of cardiovascular adverse events via post-marketing surveillance. New information on the cardiovascular risk of NSAIDs, if obtained either in Japan or elsewhere, should be promptly provided to healthcare professionals, etc.

4.(iii).B.(2).4) Adverse events at the application site
The applicant's explanation about adverse events observed at the application site:
Tables 29 and 30 show the main adverse events at the application site observed in the 2-week OA studies and in the long-term study. A causal relationship to the study drug could not be ruled out for most of the events.

The incidence of adverse events in the long-term study by treatment duration is shown in Table 22. Among the adverse events occurring at 141 sites by Week 52, events at 77 sites occurred by Week 12 and those at 34 sites by Week 8. Thus, adverse events at the application site did not tend to increase with increased treatment duration. The incidence of adverse events by application site[40] was 35.3% to 50.0%, showing no major difference among evaluation sites.

In the 2-week OA studies, adverse events occurred more frequently in the esflurbiprofen groups (the 0 mg [vehicle] group, the esflurbiprofen ≤20 mg group, and the 40 mg group) than in the FP gel patch group. The applicant provided the following explanation: Compared with gel patches, plasters require greater force to remove and therefore cause greater physical skin irritation; this suggests that repeated application and removal of esflurbiprofen plasters caused damage to skin, resulting in the higher incidence of adverse events at application site of esflurbiprofen plaster. The incidence of adverse events in the esflurbiprofen 40 mg group was comparable to that in the vehicle group, and no clear dose-response relationship was observed in the incidence. These results suggested that dermal adverse events were not caused by esflurbiprofen (the active ingredient of Loqoa Tape), but primarily by skin damage due to repeated application and removal of plasters.

[40] Adverse events in the knee joint, lumbar vertebrae, and other sites (shoulder joint, elbow joint, hip joint, foot joint, thoracic vertebrae, and hallux joint) were counted separately.

Many of the events observed with esflurbiprofen were mild in severity. Events with moderate severity were application site dermatitis (0.7% [4 of 552 subjects]) in the esflurbiprofen 40 mg group of the 2-week OA studies and application site dermatitis (4.3% [13 of 301 sites]) and application site erythema (0.7% [2 of 301 sites]) in the long-term study. No severe or serious events occurred. In both the 2-week OA studies and long-term study, many of the events resolved during the treatment period or within 2 weeks after the end of the treatment. In the 2-week OA studies, no adverse events lasted for >4 weeks, whereas in the long-term study, adverse events at 18 of 143 sites lasted for >4 weeks. Among the adverse events (at 143 sites) in the long-term study, treatment with esflurbiprofen was continued at 80 sites, discontinued at 13 sites, and interrupted at 67 sites. Esflurbiprofen was re-applied to 48 of the 67 interrupted sites. Adverse events recurred at 17 of the 48 sites after re-application, but the severity worsened only at 1 site.

Table 29. Incidence of adverse events at the application site in the 2-week OA studies

	Vehicle (292 subjects)	Esflurbiprofen ≤20 mg (638 subjects)	Esflurbiprofen 40 mg (552 subjects)	FP gel patch (317 subjects)
Adverse events at the application site	29 (9.9)	60 (9.4)	61 (11.1)	5 (1.6)
Application site dermatitis	11 (3.8)	25 (3.9)	25 (4.5)	2 (0.6)
Application site erythema	12 (4.1)	17 (2.7)	15 (2.7)	0
Application site pruritus	4 (1.4)	7 (1.1)	9 (1.6)	1 (0.3)
Application site eczema	1 (0.3)	1 (0.2)	8 (1.4)	1 (0.3)
Application site rash	1 (0.3)	9 (1.4)	7 (1.3)	1 (0.3)
Application site bruise	1 (0.3)	1 (0.2)	1 (0.2)	0
Application site haemorrhage	0	1 (0.2)	1 (0.2)	0
Rash	0	0	1 (0.2)	0
Application site irritation	0	1 (0.2)	0	0
Application site warmth	1 (0.3)	0	0	0

Number of subjects (%)

Table 30. Incidence of adverse events at the application site in the long-term study

	Esflurbiprofen 40 mg (101 subjects)	Esflurbiprofen 80 mg (100 subjects)	Sites treated with esflurbiprofen 40 mg (301 sites)
Adverse events at the application site	55 (54.5)	46 (46.0)	143 (47.5)
Application site dermatitis	34 (33.7)	27 (27.0)	88 (29.2)
Application site eczema	12 (11.9)	11 (11.0)	32 (10.6)
Application site erythema	5 (5.0)	7 (7.0)	17 (5.6)
Application site pruritus	9 (8.9)	1 (1.0)	10 (3.3)
Application site urticaria	3 (3.0)	0	3 (1.0)
Application site discolouration	1 (1.0)	1 (1.0)	3 (1.0)
Food allergy	0	1 (1.0)	2 (0.7)
Herpes simplex	0	1 (1.0)	2 (0.7)
Application site erosion	1 (1.0)	0	1 (0.3)
Excoriation	1 (1.0)	0	1 (0.3)
Dermatitis contact	1 (1.0)	0	1 (0.3)

Number of subjects or sites (%)

PMDA's view:

Many of the skin symptoms at the application site were mild and recovered soon after the end of application, so that the patients with the symptoms could continue application or re-application of study drug. Therefore, skin symptoms at the application site are controllable. However, the incidence of adverse events at application site was higher in subjects treated with esflurbiprofen plaster than in those treated with FP gel patch, suggesting that esflurbiprofen has a higher risk of application site skin symptoms than the approved patch formulations. Therefore, the applicant should issue precautionary statements to ensure that patients are closely monitored for adverse events at the application site, and that adverse events occurring in patients treated with esflurbiprofen should be managed by appropriate measures (e.g., treatment interruption) depending on the symptoms. Also, the applicant should

continuously monitor the incidence of adverse events at the application site in routine clinical use via post-marketing surveillance.

4.(iii).B.(2).5) Photosensitivity

The applicant's explanation about the possibility of photosensitivity caused by the application of esflurbiprofen:

Some NSAID patches induce serious photosensitivity (Takayama K et al. Clinical practice guideline for contact dermatitis [in Japanese]. *The Japanese journal of dermatology*. 2009;119:1757-1793), and benzophenone structure is involved in photoallergic reaction (Bagheri H et al. *Drug Saf*. 2000;22:339-349).

Neither the active ingredient nor the excipients of Loqoa Tape has a benzophenone structure. In the toxicity studies using animals or cells, esflurbiprofen did not cause changes suggestive of phototoxicity or photosensitivity [see "3.(iii).A.(7) Other toxicity studies]. In the clinical studies of esflurbiprofen conducted so far, subjects were not required to avoid outdoor activities or to shield the application site from the sun with clothes or skin guards during daily outings. However, no photosensitivity was observed at the application site of any subjects. The incidence of dermal adverse events (skin disorders) at a non-application site was 1.3% (8 of 638 subjects) with esflurbiprofen ≤20 mg, 0.5% (3 of 552 subjects) with esflurbiprofen 40 mg, 0.9% (3 of 317 subjects) with FP gel patch, and 1.4% (4 of 292 subjects) with vehicle in the 2-week OA studies, and 8.9% (9 of 101 subjects) in the esflurbiprofen 40 mg group and 14.0% (14 of 100 subjects) in the 80 mg group in the long-term study. Photosensitivity was observed in 1 subject receiving esflurbiprofen 80 mg in the long-term study, but this adverse event was considered due to sunburn, with no relationship to esflurbiprofen.

The above results do not suggest any concern about photosensitivity caused by esflurbiprofen. It is therefore unnecessary to issue precautions statements regarding photosensitivity.

PMDA's view:

At present, no data suggest a risk of photosensitivity associated with esflurbiprofen. However, the applicant should further investigate the risk of esflurbiprofen-induced photosensitivity via post-marketing surveillance, for the following reasons: (a) Only a limited number of subjects received long-term treatment with esflurbiprofen in clinical studies. (b) Only a small number of subjects received application of esflurbiprofen to skin exposed to sunlight. (c) Photosensitivity may have been involved in the adverse events at the application site (e.g., urticaria and erythema) observed in the clinical studies.

4.(iii).B.(2).6) Safety of the combination of esflurbiprofen and other NSAIDs

The applicant's explanation about the safety of the combination of esflurbiprofen and other NSAIDs:

In the long-term study, subjects were allowed to use oral, intravenous, or suppository NSAIDs for ≤14 consecutive days only for the treatment of headache, toothache, menses painful, etc. Table 31 shows the incidence of adverse events in subjects receiving esflurbiprofen with or without concomitant NSAIDs (except for topical dermal NSAIDs). The incidence of adverse events tended to be higher in subjects receiving concomitant NSAIDs (mean total days of treatment with concomitant NSAIDs: 10.6 ± 9.4 days in the 40 mg group; 8.3 ± 9.2 days in the 80 mg group; 9.5 ± 9.3 days in the 40 and 80 mg groups combined) than in those not receiving concomitant NSAIDs. Adverse events such as gastrointestinal disorders, gastrointestinal ulcer, and cardiovascular disorders tended to occur more frequently in subjects receiving concomitant NSAIDs.

In clinical studies, short-term concomitant use of other NSAIDs did not cause any clinically significant safety problems. However, the applicant will caution healthcare professionals and patients against using esflurbiprofen in combination with systemic NSAIDs (i.e., other than topical NSAIDs), because data have suggested that the systemic exposure following application of 2 plasters of 40 mg esflurbiprofen was higher than the systemic exposure following application of a FP patch, and was comparable to the systemic exposure following administration of oral FP or intravenous FP-ax.

Table 31. Incidence of adverse events with and without concomitant NSAIDs in the long-term study

	With NSAIDs		Without NSAIDs	
	Esflurbiprofen 40 mg (N = 43)	Esflurbiprofen 80 mg (N = 43)	Esflurbiprofen 40 mg (N = 58)	Esflurbiprofen 80 mg (N = 57)
Adverse events	43 (100.0)	42 (97.7)	50 (86.2)	53 (93.0)
Serious adverse events	0	2 (4.7)	3 (5.2)	3 (5.3)
Adverse events leading to discontinuation	2 (4.7)	2 (4.7)	6 (10.3)	5 (8.8)
Adverse drug reactions	23 (53.5)	26 (60.5)	32 (55.2)	26 (45.6)
Adverse events at the application site	23 (53.5)	24 (55.8)	32 (55.2)	22 (38.6)
Gastrointestinal disorders	12 (27.9)	9 (20.9)	9 (15.5)	14 (24.6)
Gastrointestinal ulcer-related events	4 (9.3)	5 (11.6)	3 (5.2)	4 (7.0)
Renal function-related events	1 (2.3)	5 (11.6)	3 (5.2)	3 (5.3)
Cardiovascular system-related events	4 (9.3)	4 (9.3)	0	1 (1.8)

n (%)

PMDA's view:
The systemic exposure following application of 2 plasters of 40 mg esflurbiprofen was higher than the systemic exposure following application of FP patch, and was comparable to the systemic exposure following administration of oral FP or intravenous FP-ax [see "4.(ii) Summary of clinical pharmacology studies"]. This suggests that the combination of esflurbiprofen and systemic NSAIDs may increase the risk of adverse events common to NSAIDs. Therefore, the applicant should caution healthcare professionals and patients against using esflurbiprofen in combination with systemic NSAIDs.

4.(iii).B.(3) Indication
PMDA has concluded that the indication of esflurbiprofen should be "relief of pain and inflammation associated with osteoarthritis," based on its review presented in "4.(iii).B.(1) Efficacy" and "4.(iii).B.(2) Safety," and based on the wording of the indication of FP patches (because the active ingredient of Loqoa Tape is the active entity of the approved FP patches).

4.(iii).B.(4) Dosage and administration
The applicant's explanation about the dosage and administration of esflurbiprofen:
The Japanese late phase II study (b) in patients with knee OA (Study 02-OA03) investigated the dose-response relationship of esflurbiprofen 10, 20, and 40 mg. The primary efficacy endpoint was the change in VAS of knee pain when standing up from a chair; according to paired comparisons between vehicle and esflurbiprofen 10, 20, or 40 mg, esflurbiprofen 40 mg showed the largest and statistically significant difference from vehicle in the change in VAS. (P = 0.001, ANCOVA model with baseline and treatment group as explanatory variables). The Japanese phase III study (Study 03-OA01) demonstrated the superiority of esflurbiprofen 40 mg to FP gel patch in the change in VAS. In the clinical studies in healthy adults, following a single administration of esflurbiprofen 40 and 80 mg (2 plasters of 40 mg) for 24 hours, plasma concentration of unchanged esflurbiprofen was maintained at a certain level up to 24 hours after the beginning of application. In the clinical studies in patients with OA, no patients received application of more than 2 plasters simultaneously, because the systemic exposure following application of 2 plasters of 40 mg esflurbiprofen is greater than the systemic exposure following application of FP patch and comparable to the exposure following administration of oral FP or intravenous FP-ax. As a result, no clinically significant safety problem occurred in patients treated with once-daily application of ≤2 plasters of 40 mg esflurbiprofen.

Thus, the applicant has proposed the following dosage and administration for Loqoa Tape (containing 40 mg esflurbiprofen per plaster): "Apply Loqoa Tape to affected area once daily. Do not apply more than 2 plasters per day." In addition, the Precautions for Dosage and Administration section of the package insert will include the following precautionary statements: (a) The systemic exposure following application of 2 plasters of Loqoa Tape is similar to the systemic exposure following administration of the usual dose of oral FP. (b) Do not apply more than 2 plasters per day, because esflurbiprofen 80 mg (2 plasters) was the maximum daily dose evaluated in clinical studies.

PMDA's view:
Based on the review presented in "4.(iii).B.(1) Efficacy" and "4.(iii).B.(2) Safety," etc., PMDA has concluded that the dosage and administration of Loqoa Tape (containing 40 mg esflurbiprofen per plaster) should be "once daily application to affected area," and that more than 2 plasters should not be applied simultaneously. However, since the systemic exposure following repeated application of 2 plasters of 40 mg esflurbiprofen is comparable to the systemic exposure following administration of oral FP or intravenous FP-ax [see "4.(ii) Summary of clinical pharmacology studies"], healthcare professionals and patients should be cautioned to avoid applying more than 2 plasters simultaneously and to comply with the proper concomitant use of NSAIDs.

4.(iii).B.(5) Clinical positioning of esflurbiprofen

The applicant's explanation about the clinical positioning of esflurbiprofen:
The main objective of treatment of OA is to delay the disease progression and improve symptoms by conservative therapy, which consists of non-drug therapy (e.g., exercise therapy, weight loss, and patient education) and drug therapy. NSAIDs are mainly used in drug therapy (Oda H et al ed. *Courses in orthopedic surgery* [in Japanese]. 4th revision. Nankodo Co., Ltd.; 334-337, 2003). Oral and topical NSAID therapy are mentioned (see the paragraph below for details) in the "OARSI recommendations for the management of hip and knee osteoarthritis: OARSI evidence-based, expert consensus guidelines (adapted for Japanese patients by the Japanese Orthopaedic Association [JOA] Committee on Clinical Practice Guidelines on the Management of OA of the Knee, the Japanese Orthopaedic Association)" (Committee on Clinical Practice Guidelines on the Management of OA of the Knee, the Japanese Orthopaedic Association, April 2015).

> The assessment of oral and topical NSAID therapy by the OARSI guidelines:
> Oral NSAID therapy is strongly recommended (recommendation level A) for the treatment of knee OA. Evidence indicates that oral NSAIDs are effective for pain relief in patients with knee OA, but they have a high risk of causing gastrointestinal disorders. Topical NSAIDs are also recommended (recommendation level B). Topical NSAIDs are effective for pain relief only for 2 weeks after the beginning of treatment, and they are inferior to oral NSAIDs in efficacy in the first week of treatment. Topical NSAIDs are therefore positioned as add-on or alternative to oral NSAIDs.

Following application of esflurbiprofen to the knee of patients with knee OA, the concentration of unchanged esflurbiprofen in the synovial membrane, synovial fluid, and plasma was higher than the concentration of unchanged FP following application of FP gel patch (FP is the racemate of esflurbiprofen) [see "4.(ii).A.(1).4) Study on tissue distribution]. The systemic exposure to unchanged compound following application of 2 plasters of 40 mg esflurbiprofen was comparable to the estimated systemic exposure to unchanged compound following administration of oral FP or intravenous FP-ax [see "4.(ii) Summary of clinical pharmacology studies"]. In the long-term study (Study SFPP-03-OA02) in patients with OA, many patients remained on esflurbiprofen alone for 52 weeks, and application of ≤2 plasters at a time caused no significant safety problems. However, given the high systemic exposure during application of esflurbiprofen plasters, the applicant considers it necessary to instruct patients to adhere to the prescribed dose (up to 2 plasters) and to issue an alert similar to that for patients using the approved oral and intravenous NSAIDs.

Thus, Loqoa Tape is more effective than the approved NSAID patches, and therefore offers a new treatment option for patients with OA.

PMDA's view:
According to the OARSI guidelines, oral NSAIDs are most strongly recommended and topical NSAIDs are positioned as add-on or alternative to oral NSAIDs. Since no studies have been conducted to compare esflurbiprofen plaster and oral NSAIDs, the clinical positioning of esflurbiprofen plaster and oral NSAIDs in the treatment of OA remains to be defined in future studies. Nevertheless, since esflurbiprofen 40 mg was shown to be superior to a FP gel patch in the Japanese phase III study (Study 03-OA01) (see the review presented in "4.(iii).B.(1) Efficacy" and "4.(iii).B.(2) Safety"), esflurbiprofen may become a treatment option as a topical NSAID for the treatment of OA. However, data have suggested that (a) gastrointestinal disorders may occur more frequently with esflurbiprofen plaster than with FP patches, and that (b) the systemic exposure following application of 2 plasters of 40 mg

esflurbiprofen is higher than the systemic exposure following application of FP patch, and comparable to the systemic exposure following administration of oral FP or intravenous FP-ax. This suggests that esflurbiprofen may have a safety risk similar to that of approved oral NSAIDs. Therefore, esflurbiprofen should not be used as an add-on to oral NSAIDs. In order to ensure the proper use of esflurbiprofen plaster, patients should be advised to avoid using more than 2 plasters simultaneously and to become familiar with precautions regarding concomitant oral NSAIDs. Adequate precautionary statements should be included in the package insert, inner pouch, and information materials for patients.

4.(iii).B.(6) Post-marketing safety measures and post-marketing surveillance, etc.

The applicant's explanation about the post-marketing safety measures:

Clinical data have suggested that the systemic exposure (AUC) following repeated application of 2 plasters of 40 mg esflurbiprofen plasters is comparable to the systemic exposure (AUC) following administration of oral FP. Patients on NSAID patch therapy often use several patches depending on the number of affected sites, and may use concomitant systemic NSAIDs (Mizutani H et al. *Journal of clinical therapeutics & medicine*. 2010;26:227-240, Mizutani H et al. *Journal of clinical therapeutics & medicine*. 2010;26:727-741). Therefore, safety problems may occur if esflurbiprofen is used in the same manner as the approved NSAID patches. In order to ensure the safety of esflurbiprofen, the drug should be contraindicated in patients with gastrointestinal ulcer, serious renal impairment, or cardiac dysfunction, as with oral and intravenous NSAIDs. Further, healthcare professionals and patients should fully understand the characteristics of esflurbiprofen and the safety risk posed by inappropriate use, and they should adhere to proper use requirements (e.g., the maximum number of plasters applied simultaneously, concomitant oral NSAIDs). The applicant will issue an alert for healthcare professionals and patients through the package insert and other information materials.

Also, in order to evaluate the safety and efficacy of esflurbiprofen in routine clinical use, the applicant plans to conduct post-marketing surveillance to assess the occurrence of skin disorders at the application site, renal dysfunction, and gastrointestinal disorders, as well as the safety in combination with other NSAIDs.

PMDA's view:

Clinical data have suggested that the systemic exposure following repeated application of 2 plasters of 40 mg esflurbiprofen plasters is higher than the systemic exposure following application of FP patch, and is comparable to the systemic exposure following administration of oral FP or intravenous FP-ax. Thus, esflurbiprofen may have a safety risk comparable to that posed by oral NSAIDs. Therefore, the applicant should issue an alert regarding the safety of esflurbiprofen, for example, by contraindicating esflurbiprofen in patients with gastrointestinal ulcer, serious renal impairment, or serious cardiac function failure, as with the approved oral and intravenous NSAIDs. Patients on NSAID patch therapy are allowed to use several patches simultaneously and concomitant oral NSAIDs. In contrast, if patients on esflurbiprofen therapy use more than 2 plasters simultaneously or concomitant oral NSAIDs, their safety risk may be increased. Therefore, healthcare professionals and patients should be provided with adequate information regarding esflurbiprofen so that they can use esflurbiprofen properly by adhering to the prescribed dose and avoiding concomitant oral NSAIDs.

Also, since only a limited number of subjects were evaluated in clinical studies, post-marketing surveillance should be conducted to assess the safety and efficacy in routine clinical use (e.g., NSAID-associated risks [renal and cardiovascular adverse events], safety in elderly patients. and the long-term safety), the number of plasters used at a time, and concomitant use of NSAIDs.

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

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

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Pharmaceutical Affairs Act. On the basis

of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application data (5.3.3.2-01, 5.3.5.1-03, 5.3.5.1-04, and 5.3.5.2-01) were subjected to an on-site GCP inspection in accordance with the provisions of the Pharmaceutical Affairs Act. PMDA concluded that the clinical studies overall were conducted in compliance with GCP and that there were no obstacles to conducting its review based on the application documents submitted. PMDA identified the following problems to be solved in a study site and the sponsor, although they had no significant impact on the review of the overall clinical studies. PMDA notified the head of the site and the applicant (sponsor) of the problems.

Problems to be solved

A study site

- Protocol deviation (a prohibited concomitant drug was used)

Sponsor

- The sponsor was not aware of the protocol deviation (the use of the prohibited concomitant drug) when it should have been. The sponsor should have found out the deviation at an appropriate timing by monitoring the study site.

IV. Overall Evaluation

On the basis of the data submitted, PMDA has concluded that esflurbiprofen has efficacy in the treatment of osteoarthritis, and that esflurbiprofen has acceptable safety in view of its benefits. Esflurbiprofen, a new topical NSAID, offers a new treatment option for patients with osteoarthritis, and is thus of clinical significance. As for safety, data have suggested that the systemic exposure following application of 2 plasters of 40 mg esflurbiprofen is comparable to the systemic exposure following administration of oral FP. The applicant should therefore issue an alert similar to that for approved oral NSAIDs, and instruct healthcare professionals and patients to use esflurbiprofen properly. Cardiovascular adverse events, effects on renal function, the long-term safety etc. should be further investigated in the post-marketing settings.

PMDA considers this marketing application may be approved if esflurbiprofen is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

August 17, 2015

I. Product Submitted for Approval

[Brand name]	Loqoa Tape
[Non-proprietary name]	Esflurbiprofen/Mentha Oil
[Applicant]	Taisho Pharmaceutical Co., Ltd.
[Date of application]	October 20, 2014

II. Content of the Review

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

(1) Efficacy, indication, and dosage and administration

The expert advisors supported the conclusion by PMDA on the efficacy, indication, and dosage of esflurbiprofen described in the Review Report (1), with the following comments:

- According to the clinical practice guidelines for hip osteoarthritis (the Japanese Orthopaedic Association Committee for clinical practice guidelines, Committee for establishing the clinical practice guideline for hip osteoarthritis. *Clinical practice guideline on the management of osteoarthritis of the hip*, 2008), non-steroidal anti-inflammatory drugs (NSAIDs) are effective for relief of pain in patients with hip osteoarthritis but whether NSAIDs prevent the long-term disease progression is unknown. The applicant should therefore collect further information on the effect of esflurbiprofen on improvement of long-term outcome.

- The systemic exposure following application of 2 plasters of 40 mg esflurbiprofen plasters is comparable to the systemic exposure following administration of oral flurbiprofen (FP) or intravenous flurbiprofen axetil (FP-ax). Therefore, more than 2 plasters should not be applied simultaneously. Healthcare professionals and patients should be instructed to use esflurbiprofen properly.

PMDA's view:
No clinically significant safety problems have been reported with FP (the racemate of esflurbiprofen), in relation to the long-term prevention effect of NSAIDs on the progression of hip osteoarthritis. No specific risk of the long-term esflurbiprofen therapy has been suggested. However, because the long-term esflurbiprofen therapy has been studied in a limited number of subjects, the applicant should collect information on the long-term esflurbiprofen therapy for osteoarthritis via post-marketing surveillance. The applicant should continue to collect information (including data from the literature) on the long-term effect of NSAIDs on the progression of osteoarthritis, and provide the obtained information to healthcare professionals in an appropriate manner.

(2) Safety and risk management plan (draft)

The expert advisors supported the conclusion by PMDA on the safety of esflurbiprofen described in the Review Report (1), with the following comments:

- The systemic exposure following application of 2 plasters of 40 mg esflurbiprofen plasters is comparable to the systemic exposure following administration of oral FP or intravenous FP-ax. This suggests that esflurbiprofen may pose a safety risk comparable to that posed by the approved oral or intravenous NSAIDs. Osteoarthritis often affects elderly patients, who often suffer from renal

impairment. The clinical experience with the approved patch formulations suggests that overdose may occur if esflurbiprofen is used in the same manner as the approved patches. Therefore, the applicant should advise healthcare professionals and patients to be very careful about the indication, the maximum permitted dose, concomitant other NSAIDs, etc.

- Healthcare professionals and patients should be instructed to avoid, as much as possible, using concomitant NSAIDs designed for systemic delivery (e.g., oral, intravenous, and suppository formulations).

- Before the launch of esflurbiprofen, the applicant should ensure that the package insert and other information materials include precautionary statements regarding gastrointestinal disorder, renal dysfunction, and cardiovascular disorders (which are the risks associated with oral and intravenous NSAIDs), as with the package inserts for oral FP and intravenous FP-ax. The applicant should further investigate the occurrence of these disorders via post-marketing surveillance.

Based on its review presented in "4.(iii).B.(2) Safety" and "4.(iii).B.(6) Post-marketing safety measures and post-marketing surveillance, etc." of the Review Report (1) and the comments raised by the expert advisors at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for esflurbiprofen should include the safety and efficacy specifications presented in Table 32, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 33.

Table 32. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Skin disorders at the application site • Adverse effects on fetus, such as ductus arteriosus systole • Renal dysfunction • Gastrointestinal disorder • Induction of asthmatic attack (aspirin asthma)	• Cardiovascular disorder • Shock, anaphylaxis • Aplastic anaemia • Toxic epidermal necrolysis, oculomucocutaneous syndrome, dermatitis exfoliative • Consciousness disturbed, seizures with loss of consciousness	• None
Efficacy specification		
• Efficacy against osteoarthritis in routine clinical use		

Table 33. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey	• Disseminate data gathered during early post-marketing phase vigilance • Preparation and distribution of "information materials for healthcare professionals" • Preparation and distribution of "information materials for patients" • A precautionary statement regarding the proper use esflurbiprofen is printed on the aluminum inner bag and liner of Loqoa Tape.

Based on the above, PMDA instructed the applicant to conduct post-marketing surveillance to investigate the safety and efficacy specifications.

The applicant's explanation:
As shown in Table 34, a specified use-results survey will be conducted in patients with osteoarthritis, with a planned sample size of 3000 patients (the safety analysis population) and a 1-year observation period. Key survey items are gastrointestinal disorder, renal dysfunction, cardiovascular disorder, skin disorder, and the safety in combination with other NSAIDs. The survey will investigate the safety and efficacy of esflurbiprofen in routine clinical use, including the safety in the elderly and in long-term treatment.

Table 34. Outline of specified use-results survey (draft)

Objective	To evaluate the safety and efficacy of esflurbiprofen in routine clinical use
Survey method	Central registration method
Population	Patients with osteoarthritis
Observation period	1 year
Planned sample size	3000 (safety analysis set)
Key survey items	Gastrointestinal disorder, renal dysfunction, cardiovascular disorder, skin disorder, safety in combination with other NSAIDs
Main survey items	• Patient characteristics (age, body weight, affected area, disease duration, prior treatment, complications, etc.) • Exposure to esflurbiprofen • Concomitant medications/therapies • Adverse events • Efficacy evaluation • Laboratory data

PMDA considers that the survey should be conducted promptly and the information obtained from the survey should be provided to healthcare professionals appropriately.

III. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the following indication and the dosage and administration, with the following conditions. Since the product is a drug with a new active ingredient, the re-examination period is 8 years. The drug substance (esflurbiprofen) is classified as a poisonous drug and the drug product as a powerful drug. The drug product is not classified as a biological product or a specified biological product.

[Indication] Relief of pain and inflammation associated with osteoarthritis

[Dosage and administration] Apply Loqoa Tape to affected area once daily. Do not apply more than 2 plasters simultaneously.

[Conditions of approval] The applicant is required to develop and appropriately implement a risk management plan.