SUMMARY OF PRODUCT CHARACTERISTIC
(with Cross-References)

1. NAME OF THE MEDICINAL PRODUCT

LOCOA 40 mg transdermal patch

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

A 10 × 14 cm patch (plaster: 1.73 g/140 cm^2) contains 40 mg of esflurbiprofen.
For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Colorless to light yellow plaster patch with a characteristic odor. The plaster, with its top covered by a liner, is spread on a support.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Relief of pain and inflammation associated with osteoarthritis

4.2 Posology and method of administration

Posology
LOCOA should be applied to the affected area once daily in adults. LOCOA more than 2 patches cannot be used at once.

Do not use more than 2 patches per day, since LOCOA is a topical patch with improved transdermal absorption and enhanced penetration of esflurbiprofen, the active ingredient, into the affected tissue. Also, the safety of LOCOA has been examined for up to 2 patches per day in clinical studies. The use of LOCOA with any other anti-inflammatory agent with expected systemic effects should be avoided wherever possible. If such use is deemed necessary, it should be limited to a minimal level and the condition of the patient should be carefully monitored.

Elderly
Since elderly patients are more susceptible to adverse reactions, their condition should be carefully monitored during treatment.

Paediatric population
Safety has not been established in low-birth-weight babies, neonates, nursing infants, infants and children. [Clinical studies have only been performed in adults and there is no experience in the use for the above patients.]

Method of administration
LOCOA is applied to the affected area.
LOCOA cannot be applied to the damaged skin or membrane and to the area of eczema or rash.
Careful administration is required with attention to the skin condition of the application site. LOCOA should be detached slowly and carefully to prevent any damage to the skin.

4.3 Contraindications

- Patients with peptic ulcer (See section 4.4) [Gastric mucosal barrier decreased by inhibition of prostaglandin synthesis may aggravate peptic ulcer.]
- Patients with severe blood abnormality [Blood disorder may develop, aggravating blood abnormality.]
- Patients with severe liver disorder [Abnormal hepatic function may develop, aggravating liver disorder.]
- Patients with severe renal disorder [Renal blood flow decreased by inhibition of prostaglandin synthesis, among others, may aggravate renal disorder.]
- Patients with severe cardiac dysfunction [Water and sodium retention induced by inhibition of prostaglandin synthesis may aggravate cardiac dysfunction.]

- Patients with severe hypertension [Water and sodium retention induced by inhibition of prostaglandin synthesis may further increase blood pressure.]
- Patients with a history of hypersensitivity to the components of LOCOA or flurbiprofen.
- Patients with current or previous aspirin-induced asthma (asthmatic attacks induced by nonsteroidal anti-inflammatory analgesics and other relevant drugs) [Asthmatic attacks may be induced.]
- Patients on enoxacin hydrate, lomefloxacin, norfloxacin, or prulifloxacin(See section 4.5.)
- Women in late pregnancy (See section 4.6.)

4.4 Special warnings and precautions for use

General
- A thorough health interview should be performed to predict hypersensitivity reactions.
- For long term use, periodic laboratory tests (urine analysis, blood test, liver function test, etc.) should be performed. If any abnormality is observed, appropriate measures such as dose interruption should be taken.
- Special attention should be paid to elderly patients with high fever or patients with wasting disease after receiving LOCOA, since symptoms such as excessive decrease in body temperature, collapse, and cold extremities may occur.
- The use of LOCOA with new quinolone antibiotics, other than enoxacine hydrate, lomefloxacin, norfloxacin and prulifloxacin (See section 4.3.), should be avoided wherever possible.
- If cutaneous symptoms are observed with the use of LOCOA, appropriate measures such as drug interruption or discontinuation should be taken according to symptoms.
- Temporary infertility has been reported in women after long term use of nonsteroidal anti-inflammatory analgesics.

Careful administration
LOCOA should be administered with care in the following patients.

Patients with peptic ulcer induced by long term use of nonsteroidal anti-inflammatory analgesics who need long term use of LOCOA and are being treated with agents such as misoprostol
Since some patients may have peptic ulcer resistant to agents such as misoprostol, adequate monitoring and careful administration is required, when the use of LOCOA is continued.

Patients with a history of peptic ulcer
Gastric mucosal barrier decreased by inhibition of prostaglandin synthesis may cause a relapse of peptic ulcer.

Patients with current or previous blood abnormality
Blood abnormality may be aggravated or recur by development of blood disorder.

Patients with bleeding tendency
Platelet function may decrease, increasing bleeding tendency.

Patients with current or previous liver disorder
Liver disorder may be aggravated or recur by hepatic function abnormality.

Patients with current or previous renal disorder, or reduced renal blood flow
Renal disorder may be aggravated or recur, or may be induced by reduced renal blood flow via inhibition of prostaglandin synthesis.

Patients with abnormal cardiac function
Water and sodium retention induced by inhibition of prostaglandin synthesis may aggravate cardiac dysfunction.

Patients with hypertension
Water and sodium retention induced by inhibition of prostaglandin synthesis may further increase blood pressure.

Patients with bronchial asthma
Some patients with bronchial asthma may actually have aspirin-induced asthma, with which asthmatic attacks may be induced.

Patients with ulcerative colitis

Symptoms aggravated by other nonsteroidal anti-inflammatory analgesics have been reported.

Patients with Crohn's disease
Symptoms aggravated by other nonsteroidal anti-inflammatory analgesics have been reported.

Use in the elderly
Elderly patients are more susceptible to adverse reactions. Care should be taken in administering LOCOA to elderly patients, for example, limiting the use to a minimal level, while special attention should be paid to possible adverse reactions.

Paediatric use
Safety has not been established in low birth weight babies, neonates, babies, infants and children. [There is no experience in the use for the above patients.]

Use this medication by prescription only.

4.5 Interaction with other medicinal products and other forms of interaction

Contraindications for concomitant administration

Enoxacin hydrate, Lomefloxacin, Norfloxacin, Prulifloxacin
Concomitant use may induce convulsions due to enhancing GABA inhibition by new quinolone antibiotics.

Precautions for concomitant administration

New quinolone antibiotics (Ofloxacin, etc.) [Note that enoxacin hydrate, lomefloxacin, norfloxacin and prulifloxacin are contraindicated for concomitant administration]
Concomitant use may induce convulsions due to enhancing GABA inhibition by new quinolone antibiotics.

Coumarin anticoagulants (Warfarin)
Care such as dose adjustment should be taken to avoid possible increase in effect of coumarin anticoagulants (warfarin). Esflurbiprofen may compete with warfarin in plasma protein binding, increasing free warfarin.

Methotrexate
Care such as dose adjustment should be taken to avoid possible poisoning symptoms (e.g., anaemia and thrombocytopenia) due to increase in the effect of methotrexate.
Inhibition of prostaglandin synthesis by esflurbiprofen may reduce renal blood flow, resulting in decreased renal excretion and thus increased blood levels of methotrexate.

Lithium products (Lithium carbonate)
Careful measures such as adequate monitoring of lithium blood levels should be taken during the use of lithium products, since concomitant use may increase blood levels of lithium, which may cause lithium poisoning symptoms. Inhibition of prostaglandin synthesis by esflurbiprofen may reduce renal excretion of sodium and lithium clearance, thus increasing lithium blood levels.

Thiazide diuretics (Hydrochlorothiazide, etc.) and loop diuretics (Furosemide, etc.)
The effect of these diuretics may decrease. Inhibition of prostaglandin synthesis by esflurbiprofen may produce water and salt retention in the body.

Corticosteroids (Methylprednisolone, etc.)
Concomitant use may mutually increase gastrointestinal reactions (peptic ulcer, gastrointestinal bleeding, etc.). Concomitant use may increase gastrointestinal reactions to both drugs.

Pharmacokinetic interaction with CYP2C9 inhibitors (Fluconazole, etc.)
Esflurbiprofen is mainly metabolized by hepatic enzyme CYP2C9. Esflurbiprofen blood levels may increase, since metabolism of esflurbiprofen is inhibited by concomitant use of CYP2C9 inhibitors.

Tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, Ginkgo, and Low molecular weight heparins
Concomitant use may result in an increased risk of bleeding.

Cyclosporine
Concomitant use may result in an increased risk of cyclosporine nephrotoxicity.

Tenofovir disoproxil fumarate, tacrolimus
Concomitant use may result in increased risk of acute renal failure.

Potassium sparing diuretics
Concomitant use may result in reduced diuretic effectiveness, hyperkalemia, or possible nephrotoxicity.

4.6 Fertility, pregnancy and lactation

- LOCOA cannot be used in women in late pregnancy. A study in rats in late pregnancy showed deaths of dams, delayed delivery, reduced fertility rates, and increased stillbirths with less than the plasma esflurbiprofen level (AUC) equivalent to that yielded by the use of 2 patches of LOCOA in humans (See section 5.3.)
- LOCOA should be used in pregnant women (other than those in late pregnancy) or potentially pregnant women, only if therapeutic benefits are deemed to outweigh risks. [Safety has not been established in pregnant women.]
- The use of LOCOA should be avoided in lactating women. If such use is deemed necessary, they should use it after the patient has stopped lactating. [An animal study (rats) showed excretion of esflurbiprofen into the milk and restricted increase in body weight in offspring of dams with approximately 3 times the plasma level (AUC) yielded by the use of 2 patches of LOCOA in humans (See section 5.3.)]
- Constriction of the fetal ductus arteriosus has been reported in women in late pregnancy using other topical nonsteroidal anti-inflammatory analgesics.
- Temporary infertility has been reported in women after long term use of nonsteroidal anti-inflammatory analgesics.

4.7 Effects on ability to drive and use machines

It is considered that application of LOCOA at recommended doses has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
In the clinical studies performed in a total of 1,391 patients, 415 adverse reactions were reported in 269 patients (19.3%), including application site dermatitis in 111 patients (8.0%), application site erythema in 44 patients (3.2%), and application site eczema in 32 patients (2.3%).

Tabulated list of adverse reactions reported in the clinical studies and from post-marketing experience
The following adverse reactions have been reported in all the clinical trials and from post-marketing experience with LOCOA. Adverse reactions listed below are classified according to frequency and system organ class (SOC).

Table 1. Adverse reactions in all the clinical trials and from post-marketing experience with LOCOA

	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Incidence unknown
Application site disorders	Dermatitis, Erythema, Pruritus, Eczema, Rash	Bruise, Irritation	Oedema
Nervous system disorders		Dizziness	Headache
Gastrointestinal disorders		Abdominal discomfort, Gastritis, Peptic ulcer, Abdominal pain, Nausea, Vomiting, Stomatitis	Constipation, Diarrhoea, Decreased appetite
Hypersensitivity		Rash	Angioedema (face, eyelid, etc.), Eczema, Erythema, Urticaria, Flushing

Investigations	Blood urea increased	Blood creatinine increased, AST (GOT) increased, ALT (GPT) increased, Blood urine present, Blood bilirubin increased, Blood lactate dehydrogenase increased, Urine glucose present, Urine protein positive	Blood pressure increased
Others		Palpitations	Oedema peripheral

Clinically significant adverse reactions

Shock, anaphylaxis
Since shock and anaphylaxis have been reported (with an unknown incidence for both) with the use of esflurbiprofen, the condition of patients,should be carefully monitored, and treatment should be discontinued while taking appropriate actions if symptoms such as chest discomfort, chills, cold sweat, dyspnea, numbness in extremities, decreased blood pressure, angioedema, and urticaria are observed.

Acute kidney injury, nephrotic syndrome
Since acute kidney injury has been reported (with an unknown incidence) with the use of esflurbiprofen, this medicine may cause serious renal disorders including acute kidney injury and nephrotic syndrome. So the condition of patients should be carefully monitored, for example, with periodic tests, and appropriate actions should be taken such as discontinued treatment, if signs such as oliguria, hematuria, protein urine, increases in BUN and blood creatinine, hyperkalaemia, and hypoalbuminaemia are observed.

Gastrointestinal bleeding
Since gastrointestinal bleeding has been reported (with an unknown incidence) with the use of esflurbiprofen, the condition of patients should be carefully monitored, and treatment should be discontinued while taking appropriate treatment, if any abnormality is observed.

Aplastic anaemia
Since aplastic anaemia has been reported (with an unknown incidence) with the use of oral flurbiprofen, the condition of patients should be carefully monitored, and appropriate actions should be taken such as discontinued treatment.

Induced asthma attacks (aspirin-induced asthma)
Since asthma attacks have been induced by the use of esflurbiprofen, treatment should be discontinued if initial symptoms such as dry rales, wheezing, and dyspnea are observed.

Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, exfoliative dermatitis
Since Stevens-Johnson syndrome has been reported (with an unknown incidence) with the use of esflurbiprofen, this medicine may cause toxic epidermal necrolysis, Stevens-Johnson syndrome, and exfoliative dermatitis. So the condition of patients should be carefully monitored and treatment should be discontinued while taking appropriate treatment, if any abnormality is observed.

Impaired consciousness, convulsions with impaired consciousness
Since impaired consciousness and convulsions with impaired consciousness have been reported (with an incidence of < 0.1%) with the use of flurbiprofen axetil [injections], the condition of patients should be carefully monitored, and treatment should be discontinued while taking appropriate treatment, if any abnormality is observed.

4.9 Overdose [1)]

Symptoms
Symptoms of overdose may include headache, nausea, vomiting, epigastric pain, gastrointestinal bleeding, rarely diarrhea, disorientation, excitation, coma, drowsiness, dizziness, tinnitus, fainting and occasionally convulsions. In cases of significant poisoning, acute renal failure and liver damage are possible.

Therapeutic measures
Patients should be treated symptomatically as required.
Patients should immediately remove the patches and wash the skin with water, then contact the doctor, pharmacist, or nearest hospital immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action [2)]
Esflurbiprofen is an optical isomer (S isomer) of flurbiprofen, racemate.
An *in vitro* study demonstrated the inhibitory action of esflurbiprofen on the cyclooxygenase activity, which is probably the main source of anti-inflammatory/analgesic effects.

Pharmacodynamic effects
Analgesic effect [3)]
The analgesic effect was demonstrated in all pain models: a dog model of urate-induced knee joint arthritic pain, and rat models of carrageenan-induced inflammatory pain, silver nitrate-induced arthritic pain, and adjuvant-induced arthritic pain.

Anti-inflammatory effect [4)]
The anti-inflammatory effect was demonstrated in all acute inflammation models: rat models of carrageenan-induced footpad inflammation, traumatic oedema, and adjuvant-induced arthritis.

Clinical efficacy and safety [5), 6)]
A randomized double-blind, placebo-controlled, parallel-group study (phase II dose-finding study) and a randomized open-label* parallel-group study with flurbiprofen patches as the control (phase III study) were performed in patients with knee osteoarthritis. The following tables show changes from baseline in VAS scores (pain felt on rising from the chair) in patients receiving esflurbiprofen 40 mg, base, or flurbiprofen patches for 2 weeks.
*The study was performed with well managed information on treatment groups for study subjects and investigators.

Table 2. Phase II dose-finding study

	10 mg	20 mg	40 mg	Base
Baseline	57.8 ± 12.3 (121)	56.0 ± 12.5 (127)	57.0 ± 12.4 (134)	58.4 ± 13.5 (126)
Final evaluation	26.1 ± 17.5 (121)	24.5 ± 17.6 (127)	21.5 ± 16.7 (134)	28.4 ± 18.9 (126)
Change	-31.7 ± 17.1 (121)	-31.5 ± 16.1 (127)	-35.5 ± 17.1 (134)	-30.1 ± 18.8 (126)
Between-group difference[a)] [95% confidence interval][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 (mm) ± SD (No. of subjects)
a) An analysis of covariance model with explanatory variables of baseline and treatment group (one-sided significance level 0.025)
b) The fixed order approach was used to take multiplicity of the test into account in paired comparisons of the esflurbiprofen 40, 20, and 10 mg groups and the base group.

Table 3. Phase III study

	Esflurbiprofen 40 mg	Flurbiprofen patch 40mg x 2
Baseline	59.5 ± 12.7 (315)	59.3 ± 12.5 (317)
Final evaluation	18.5 ± 15.3 (315)	28.8 ± 18.1 (317)
Change	-41.0 ± 15.5 (315)	-30.5 ± 15.9 (317)
Between-group difference[a)] [95% confidence interval][a)] p-value[a)]	-10.4 [-12.7, -8.0] p<0.001	-

Mean (mm) ± SD (No. of subjects)
a) An analysis of covariance model with explanatory variables of baseline and treatment group (one-sided significance level 0.025)

5.2 Pharmacokinetic properties

Plasma Levels

Single dose [7)]

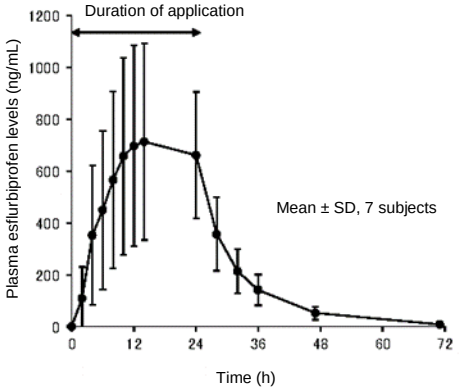
The pharmacokinetic parameters and changes in plasma concentrations in healthy adults (Japanese) receiving a single 24-hour application of 40 mg of esflurbiprofen are shown in Table 4 and Figure 1. Based on the residual drug amount in the patch, the transdermal absorption was calculated to be 48.34 ± 16.70%.

Table 4. Pharmacokinetics parameters of esflurbiprofen after a single administration

Dose (No. of subjects)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (ng·h/mL)
40 mg (7 subjects)	751 ± 360	17.7 ± 5.94	8.60 ± 0.615	19000 ± 9390

Mean ± SD

Figure 1. Plasma concentration-time profile of esflurbiprofen after a single 24-hour application of 40 mg of esflurbiprofen in human



Multiple doses [8)]

The pharmacokinetic parameters in healthy adults (Japanese) receiving multiple 23-hour applications of once daily doses of 80 mg of esflurbiprofen for 7 days are shown in Table 5. Based on the residual drug amount in the patch, the transdermal absorption was calculated to be 73.24 ± 11.58%.

Table5. Pharmacokinetics parameters of esflurbiprofen after multiple administration

Dose (No. of subjects)	Study day	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC_{0-23h} (ng·h/mL)
80 mg (6 subjects)	Day 1	1360 ± 551	10.3 ± 1.51	-	23500 ± 8530
	Day 7	2710 ± 669	6.67 ± 2.07	8.13 ± 0.503	47000 ± 10100

Mean ± SD, -: No data

Distribution

Tissue penetration [9)]

In patients (Japanese) with knee osteoarthritis scheduled to undergo knee replacement arthroplasty, the levels of esflurbiprofen in the synovia, synovial fluid, and plasma after a single 12-hour application of 20 mg of esflurbiprofen were 14.8, 32.7, and 34.5 times higher, respectively, than those after the use of 40 mg flurbiprofen patch.

Protein binding [10)]

An *in vitro* study showed that 99.95% of esflurbiprofen was bound to human plasma protein, probably to albumin as the main binding protein.

Metabolism [11), 12)]

Esflurbiprofen mainly undergoes oxidative metabolism by CYP2C9. A study investigating the effect of CYP2C9 polymorphism using human liver microsomes showed the 4'-hydroxylation activity (CL_{int}) in poor metabolizers (PMs) (with genotype CYP2C9*3/*3) was 1/69 of that in extensive metabolizers (EMs) (with genotype CYP2C9*1/*1).

Excretion [8), 13)]

In healthy adults (Japanese) receiving a single 24-hour application of 80 mg of esflurbiprofen, little of the dose (0.253%) was excreted as unchanged compound in the urine through 72 hours after the start of application.
Major metabolites were glucuronate or sulfate conjugates of the 4'-hydroxy compound. Other metabolites were free glucuronate conjugates, 4'-hydroxy compounds, and glucuronate conjugates of the 3'-hydroxy-4'-methoxy compound.

5.3 Preclinical safety data [14), 15)]

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, fertility and early development, and embryo-fetal development.

In the pre- and postnatal development study using rats in late pregnancy, maternal animal death at ≥ 0.1 mg/kg, a tendency of an increased number and percentage of stillborn pups at 0.1, 0.3, and 3 mg/kg, delayed delivery at 0.3 mg/kg, reduced live birth index at ≥ 0.3 mg/kg, and incomplete delivery and prolonged delivery at ≥ 1 mg/kg were indicated. Since the $AUC_{0\text{-}24h}$ value of esflurbiprofen on Day 17 of gestation at 1 mg/kg was comparable or less than the exposure after 40 or 80 mg of esflurbiprofen was administered to humans, the $AUC_{0\text{-}24h}$ values at 0.1 and 0.3 mg/kg appeared to be lower than that in humans.

After esflurbiprofen was administered to rats in the lactation period, suppression of postnatal body weight gain and delayed onset of early behavior were seen at 3 mg/kg. The $AUC_{0\text{-}24h}$ value of esflurbiprofen on Day 17 of gestation at 3 mg/kg were 5.77 and 2.55 times higher than the exposure after 40 or 80 mg of esflurbiprofen was administered to humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mentha oil
Liquid paraffin
Styrene-isoprene-styrene block copolymer
Polyisobutylene
Ester gum HG
Propylene glycol dicaprylate
2-Mercaptobenzimidazole
Dibutylhydroxytoluene

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

18 months

6.4 Special precautions for storage

Store in the original packaging at ambient. Store below 30°C

6.5 Nature and contents of container

Inner package: Aluminum composite film
Packaging: 70 patches (7 patches × 10 sachets)

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Under Authority of:
Taisho Pharmaceutical Co., Ltd.
3-24-1 Takada, Toshima-ku, Tokyo, Japan

Manufactured by:
TOKUHON Corporation Miyashiro Factory
1010, Aza Yamazaki, Miyashiro-machi, Minamisaitama-gun, Saitama, Japan

Imported by:
Osotspa Taisho Pharmaceutical Co., Ltd.
1126/2 Vanit Building II, 34th fl., Room 3401, 3404, New Petchburi Rd.,
Makkasan, Ratchathewi, Bangkok, 10400 Thailand

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Warnings (based on the Misnistry of Public Health Announcement)

1. This drug may cause skin adverse reactions. If you notice any undesirable skin reaction, should be discontinued immediately and consult a doctor.
2. Do not use in patients who have asthma, acute urticaria, or acute rhinitis, an allergy (hypersensitivity) to aspirin, or other NSAIDs.
3. Avoid using this drug during the last trimester unless under medical advice.
4. Avoid using this drug in people who have GI bleeding in the stomach, intestines or ulcers. Regarding to the drug increases the risk of these events.
5. Avoid using in patient with liver or kidney diseases and liver or kidney disorders.
6. Long-term administration of this drug may cause the same adverse events as oral NSAID drugs e.g. platelet disorders, cardiovascular disorders.
7. Should be used with caution in the elderly patients.

REFERENCES

1) Froben (Flurbiprofen) 100 mg Tablets (Mylan): Summary of Product Characteristic, Revised on 15 January 2019
https://www.medicines.org.uk/emc/product/327/smpc

2) Company data (A study on mechanism of action)

3) Company data (A study on analgesic effects)

4) Company data (A study on anti-inflammatory effects)

5) Company data (A phase II dose-finding study in patients with gonarthrosis)

6) Company data (A phase III study in patients with gonarthrosis)

7) Company data (Pharmacokinetic studies in healthy adults)

8) Company data (A high-dose safety study in healthy adults)

9) Company data (Tissue distribution study in patients with gonarthrosis)

10) Company data (A study on plasma protein binding: in vitro)

11) Tracy TS., et al.: Biochem Pharmacol. 52, 1305 (1996)

12) Company data (A study on liver microsomal metabolism: in vitro)

13) Company data (A study on single application of SFPP in healthy adults)

14) T40054, Preliminary Subcutaneous Study of Effects of S(+)-Flurbiprofen on Pre- and Postnatal Development, Including Maternal Function in Rats, Module 4.2.3.5.3

15) LD11322, Subcutaneous Study of Effects of S(+)-Flurbiprofen on Pre- and Postnatal Development, Including Maternal Function in Rats, Module 4.2.3.5.3