SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

IONSYS 40 micrograms per dose transdermal system

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each IONSYS system contains fentanyl hydrochloride equivalent to 9.7 mg of fentanyl and delivers 40 micrograms fentanyl per dose, to a maximum of 80 doses (3.2 mg/24 hours).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal system

IONSYS is composed of an electronic controller and a drug unit with two hydrogels. The controller is white with the identifier 'IONSYS®' and has a digital display, a light window, and a recessed dose activation button. The drug unit is blue on the side that connects to the controller and has a red bottom housing containing the hydrogels, one of which contains the fentanyl. The assembled IONSYS product measures 47 mm x 75 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IONSYS is indicated for the management of acute moderate to severe post-operative pain in adult patients.

4.2 Posology and method of administration

IONSYS is restricted to hospital use only. Treatment should be initiated by and remain under the guidance of a physician experienced in the management of opioid therapy. Due to the well-known potential of abuse of fentanyl, physicians should evaluate patients for a history of drug abuse (see section 4.4).

Posology

Patients should be titrated to an acceptable level of analgesia prior to initiating use of IONSYS (see section 5.1).

IONSYS should only be activated by the patient.

Each dose of IONSYS delivers 40 micrograms of fentanyl over a 10 minute period, to a maximum of 240 micrograms per hour (6 doses each of 10 minutes duration). IONSYS will operate for 24 hours after the system is assembled or for 80 doses, whichever comes first, and then becomes inoperative.

After 24 hours or 80 doses, a new system should be applied if necessary. Each new system should be placed on a new skin site. With each new IONSYS application the patient may use IONSYS more frequently than during the remainder of the 24 hour dosing period, due to a lower absorption of fentanyl from the system for the first few hours (see section 5.2).

The maximum treatment duration is 72 hours, although the majority of patients should only need one system.

Patients should not wear more than one system at a time.

Used systems should not be reapplied to a patient.

IONSYS should be removed before the patient is discharged.

Elderly patients
As with all fentanyl products, the clearance of fentanyl may be reduced in elderly patients, with a consequent increase in half life. No specific dose adjustment is required in elderly patients. However elderly patients should be observed closely for adverse effects of fentanyl (see sections 4.4 and 4.8).

Hepatic or renal impairment
IONSYS should be administered with caution to patients with moderate or severe hepatic or renal impairment (see section 4.4).

Paediatric population
The safety and efficacy of IONSYS in children and adolescents younger than 18 years of age has not been established. Currently available data are described in section 4.8, but no recommendation on posology can be made.

Method of administration

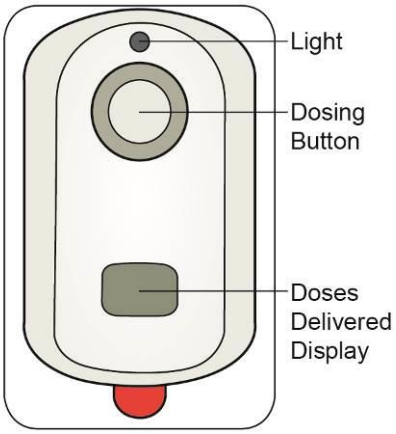
IONSYS is for transdermal use only.

Precaution to be taken before manipulating or administering the product
Gloves should be worn when manipulating IONSYS. To avoid oral ingestion of the fentanyl-containing hydrogel, which may cause life-threatening hypoventilation or death, the hydrogel must not touch the mouth or other mucosal areas.

Patients should not get IONSYS wet. Prolonged contact with water could affect system performance and cause the system to fall off.

Preparation of application site
IONSYS should be applied to intact, non-irritated and non-irradiated skin. IONSYS should not be placed on abnormal skin sites, such as scars, burns, tattoos, etc. IONSYS should also not be placed on skin on which topical medicines have been applied. Hair at the application site should be clipped (not shaved) before system application. IONSYS should not be applied to a previously used skin site. The application site should be wiped with a standard alcohol swab and the skin should be allowed to dry completely before IONSYS is applied. No soaps, oils, lotions, or any other agents that might irritate the skin or alter its absorption characteristics should be used to clean the application site.

Assembly of IONSYS
IONSYS should not be used if the seal on the tray or the sachet containing the Drug Unit is broken or damaged.



Gloves should be worn during the assembly of IONSYS. The tray is opened by pulling back on the tray lid. The sachet containing the Drug Unit should be opened starting at the pre-cut notch, then by carefully tearing along the top of the sachet. The Drug Unit should be removed from the sachet and the Controller should be snapped on by aligning the shape and firmly pressing the two parts together.

When assembled, the digital display of the Controller will complete a short self-test during which there will be an audible beep, the red light will flash once, and the digital display will flash the number 88. At the end of the self-test, the display will show the number 0 and a green light will flash at a slow rate to indicate IONSYS is ready for application.

Application of IONSYS
The clear plastic film covering the adhesive should be removed and discarded with care taken not to touch the hydrogels. IONSYS should be pressed firmly in place for at least 15 seconds with the sticky side down on the skin of the chest or upper arm of the patient. Pressure should be applied with the fingers around the outer edges to ensure adhesion to the skin site. If at any point during use the system loosens from the skin, a non-allergenic tape may be used to secure the edges to ensure complete contact with the skin. When applying tape, care should be taken not to tape over the light window, the digital display, or the dosing button. The dosing button must not be pressed.

For further details, see section 6.6.

Dose delivery
A recessed dosing button is located on the Controller of IONSYS. To initiate administration of a fentanyl dose, the patient should press and release the dosing button twice within 3 seconds. IONSYS should only be activated by the patient.

Upon successful dose initiation, IONSYS will emit a beep indicating the start of delivery. The green light will change from a slow flash rate to a rapid flash rate and the digital display will alternate between a rotating circle and the number of completed doses during the entire 10-minute dose delivery period. The next dose cannot be initiated until the previous 10-minute delivery period is complete. Pressing the button during delivery of a dose will not result in additional fentanyl being administered. After the 10-minute dose has been completely delivered, the green light will return to a slow flash rate, the digital display will show the number of doses that have been delivered, and IONSYS will be ready to be used again by the patient.

At the end of 24 hours of use, or after 80 doses have been administered, the green light will switch off and the number of doses delivered will flash on and off. The flashing digital display may be turned off by pressing the dose button for six seconds.

Removal
IONSYS is removed from the patient by lifting the system at the red tab and peeling it away from the skin site. Gloves must be worn while removing IONSYS from the skin and care should be taken to

avoid touching the hydrogels. If the medicinal product contacts the skin during removal, the contact area should be thoroughly rinsed with water without using any soap.

IONSYS may be removed at any time. However, once a system has been removed, the same system should not be reapplied. If the patient requires additional treatment for pain, a new system may be applied to a new skin site on the upper outer arm or chest.

Special precautions for disposal should be followed (see section 6.6).

Troubleshooting
Each IONSYS system is designed to deliver up to 80 10-minute doses of fentanyl over a period of 24 hours. The table below represents the different error messages that may occur, together with the probable cause and the action to be taken.

Error message/feedback	**Probable cause**	**Action required**
• No light • No beeps • No display	Low battery or defective system	1. Do not use the system 2. Dispose of system per instructions in Section 6.6 3. Place a new system on a different skin site
• Blinking red light for 15 seconds • Beeping for 15 seconds • System is not securely adhered	Poor skin contact	1. Secure system to patient's skin by pressing the edges firmly or by applying non-allergenic tape 2. If system beeps again, then remove and dispose of system, and place a new system on a different skin site.
• Continuous blinking red light • Continuous beeping • Steady display number	System error	1. Remove system from patient 2. Hold down dosing button until beeping stops and display goes blank 3. Dispose of system per instructions in Section 6.6 4. Place a new system on a different skin site
• No light • No beeps • Blinking display number	End of use at 24 hours or 80 doses	1. Remove system from patient 2. Hold down dosing button until display goes blank 3. Dispose of system per instructions in Section 6.6 4. Place a new system on a different skin site

If device failure or malfunction is suspected by a healthcare professional, IONSYS should be immediately removed from the patient and The Medicines Company contacted straightaway.

The healthcare professional must ensure the patient understands that if they suspect a device failure or malfunction, they must immediately inform a healthcare professional.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Severe respiratory depression or cystic fibrosis.

4.4 Special warnings and precautions for use

Before any surgery, the healthcare professional should ensure that the patient has been properly informed on how to use IONSYS post-operatively.

A potentially dangerous amount of fentanyl remains in the IONSYS system after use. For disposal instructions, see section 6.6.

IONSYS should be removed before a magnetic resonance imaging (MRI) procedure, cardioversion, defibrillation, X-ray, CT scan or diathermy is undertaken.

Excessive sweating may reduce delivery of fentanyl.

Respiratory depression

IONSYS should only be activated by the patient, to avoid potential overdosing.

Significant respiratory depression may occur with IONSYS; patients must be observed for these effects (see section 4.9).

The use of concomitant CNS-active medicinal products may increase the risk of respiratory depression (see section 4.5).

Chronic pulmonary disease

In patients with chronic obstructive pulmonary disease or patients with conditions pre-disposing them to hypoventilation, more severe adverse reactions may be experienced. In such patients, opioids may decrease respiratory drive and increase airway resistance.

Head injuries and increased intracranial pressure

Fentanyl should not be used in patients who may be particularly susceptible to the intracranial effects of CO2 retention, such as those with evidence of increased intracranial pressure, impaired consciousness, or coma. Opioids may obscure the clinical course of patients with head injury. Fentanyl should be used with caution in patients with brain tumours or other significant space occupying lesions of the brain.

Cardiac disease

Fentanyl may produce bradycardia or hypotension and should, therefore, be administered with caution to patients with bradyarrhythmias or any significant cardiovascular disease.

Paralytic ileus

IONSYS should be used with caution in patients with paralytic ileus.

Abuse potential and dependence

Fentanyl has a well-known abuse potential. Patients with a prior history of drug dependence/alcohol abuse are more at risk to develop dependence and abuse in opioid treatment. Physicians should evaluate patients for a history of drug abuse and follow such patients closely.

Tolerance, physical dependence, and psychological dependence may develop upon repeated administration of opioids. Iatrogenic addiction following opioid administration is rare. Fentanyl can be abused in a manner similar to other opioid agonists. Abuse or intentional misuse of IONSYS may result in overdose and/or death.

Hepatic disease

Fentanyl is metabolised into inactive metabolites in the liver. Hepatic disease may delay elimination. Patients with hepatic impairment should be observed carefully for signs of fentanyl toxicity.

Renal disease

Less than 10% of administered fentanyl is excreted unchanged by the kidney. Unlike morphine, no active fentanyl metabolites are eliminated by the kidney. Data obtained with intravenous fentanyl in patients with renal failure suggest that the volume of distribution of fentanyl may be changed by dialysis. This may affect serum concentrations. If patients with renal impairment receive IONSYS, they should be observed carefully for signs of fentanyl toxicity.

Elderly patients

Elderly patients should be observed carefully for adverse effects of fentanyl during IONSYS administration (see sections 4.2 and 4.8).

Obese patients

The overall adverse reaction profile for morbidly obese patients (BMI > 40) does not suggest a meaningful difference in safety compared to patients with BMI ≤ 40. However, caution is advised when prescribing IONSYS in morbidly obese patients because they may be at increased risk of other comorbid respiratory conditions (i.e., sleep apnoea) potentially pre-disposing them to hypoventilation or more severe adverse reactions (see section 4.8).

Hearing impairment

IONSYS should be used with caution in patients with hearing impairment who might not be able to hear the audible signals from the system.

Thoracic/chest and upper abdominal surgeries

Only limited data are available in patients with thoracic/chest and upper abdominal surgeries. IONSYS should, therefore, be used with caution in these patients.

Physical status

The safety of IONSYS has not been established in patients with American Society of Anesthesiologists (ASA) physical status classification IV (i.e. patients with a severe systemic disease that is a constant threat to life).

Patients with genetic polymorphisms affecting CYP3A4 and CYP3A5

Published literature indicates potential for increased fentanyl exposure in patients with genetic polymorphisms affecting CYP3A4 and CYP3A5, with a small variability in concentrations with transdermal administration; therefore, IONSYS should be used with caution in these patients (see section 5.2)

4.5 Interaction with other medicinal products and other forms of interaction

The concomitant use of other central nervous system depressants including other opioids, sedatives or hypnotics, general anaesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines, and alcoholic beverages, may produce additive depressant effects. Hypoventilation, hypotension, and profound sedation or coma may occur. Therefore, the use of any of these medicinal products concomitantly with IONSYS requires special patient care and observation.

Fentanyl, a high clearance active substance, is rapidly and extensively metabolised mainly by CYP3A4. Itraconazole, a potent CYP3A4 inhibitor, at 200 mg/day orally for 4 days had no significant effect on the pharmacokinetics of intravenous fentanyl. Oral ritonavir, one of the most potent CYP3A4

inhibitors, reduced the clearance of intravenous fentanyl by two thirds. The concomitant use of potent CYP3A4 inhibitors (e.g., as ritonavir, ketoconazole, itraconazole, troleandomycin, clarithromycin, and nelfinavir) or moderate CYP3A4 inhibitors (e.g., amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and verapamil) with IONSYS may result in an increase in fentanyl plasma concentrations, which could increase or prolong both the therapeutic effect and adverse reactions, and may cause serious respiratory depression. In this situation, special patient care and observation are appropriate. The concomitant use of ritonavir or other potent or moderate CYP3A4 inhibitors and IONSYS is not recommended unless the patient is closely monitored.

The concomitant use of partial opioid agonists/antagonists (e.g. buprenorphine, nalbuphine, pentazocine) is not recommended. They have high affinity to opioid receptors with relatively low intrinsic activity and therefore partially antagonise the analgesic effect of fentanyl and may induce withdrawal symptoms in opioid dependant patients.

Serotoninergic medicinal products

Co-administration of fentanyl with a serotoninergic agent, such as a Selective Serotonin Re-uptake Inhibitor (SSRI) or a Serotonin Norepinephrine Re-uptake Inhibitor (SNRI) or a Monoamine Oxidase Inhibitor (MAOI), may increase the risk of serotonin syndrome, a potentially life-threatening condition.

IONSYS is not recommended for use in patients who have received monoamine oxidase (MAO) inhibitors within 14 days because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics

Interaction studies have only been performed in adults.

Topical medicines

Application of the IONSYS system on skin on which any topical medicine has been applied should be avoided. An alternative application site should be chosen.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of fentanyl in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). IONSYS should not be used in pregnancy unless clearly necessary.

Administration during childbirth is not recommended because fentanyl crosses the placenta and the fetal respiratory centre is sensitive to opiates. If IONSYS is administered to the mother during this time, an antidote for the child should be readily available. Following long-term treatment fentanyl may cause withdrawal symptoms in the newborn.

Breast-feeding

Fentanyl is excreted into human milk. Breast-feeding is not recommended for 24 hours following removal of IONSYS.

Fertility

There are no clinical data on the effects of fentanyl on fertility. Studies in rats have revealed reduced fertility and enhanced embryo mortality (see section 5.3).

4.7 Effects on ability to drive and use machines

Opioid analgesics impair the mental and/or physical ability required for the performance of potentially dangerous tasks (e.g., driving a car or operating machinery). Patients should be advised not to drive or operate machinery if they experience somnolence, dizziness, or visual disturbance.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions were nausea, vomiting, and application site reactions such as erythema and pruritus. These were mostly of mild to moderate severity. The most serious adverse reactions reported were hypotension and apnoea and all patients should be closely monitored for these.

Tabulated list of adverse reactions

The following adverse reactions have been reported with IONSYS during clinical studies and post marketing experience. All adverse reactions are listed by System Organ Class and frequency: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); and rare (≥1/10,000 to <1/1,000).

System Organ Class	Very Common	Common	Uncommon	Rare
Infections and infestations				Rhinitis
Blood and lymphatic system disorders			Anaemia	
Metabolism and nutrition disorders			Decreased appetite	Hypocalcaemia Hypoglycaemia Hypokalaemia
Psychiatric disorders		Insomnia	Abnormal dreams Agitation Anxiety Confusional state Hallucination Nervousness	Depression Thinking abnormal thoughts
Nervous system disorders		Dizziness Headache	Migraine Paraesthesia Somnolence Syncope	Dysgeusia Hypoaesthesia
Eye disorders			Vision blurred	
Ear and labyrinth disorders				Vertigo
Cardiac disorders			Tachycardia	Bradychardia
Vascular disorders		Hypotension	Hypertension Orthostatic hypotension, Vasodilitation	
Respiratory, thoracic and mediastinal disorders		Hypoxia	Apnoea Cough Dyspnoea Hiccups Hypoventilation	Lung disorder
Gastrointestinal disorders	Nausea Vomiting	Constipation Abdominal pain	Dry mouth Dyspepsia	Abdominal distension

System Organ Class	Very Common	Common	Uncommon	Rare
			Flatulence Ileus	Diarrhoea Eructation
Skin and subcutaneous tissue disorders		Pruritus	Rash Hyperhidrosis	
Musculoskeletal and connective tissue disorders			Back pain Pain in extremity	Hypertonia Myalgia
Renal and urinary disorders		Urinary retention	Oliguria	Dysuria
General disorders and administration site conditions	Application site erythema	Application site oedema Application site pruritus Application site reaction Application site vesicles Pyrexia	Application site pain Application site dryness Application site papules Asthenia Chills Application site reaction Pain	Chest pain Malaise Application site paraesthesia Injection site oedema Injection site pain Oedema
Injury, poisoning and procedural complications				Wound complication
Surgical and medical procedures			Gastrointestinal disorder therapy	

Paediatric population

Data on IONSYS in paediatrics is limited to information from a single clinical trial. In this study 28 paediatric patients, 6 to 16 years old, were treated with IONSYS fentanyl 40 micrograms after experiencing inadequate analgesia with IONSYS fentanyl 25 micrograms. Among these patients, the incidence of nausea was similar to adult patients; however, vomiting (32.1%) and fever (60.7%) were each reported at a higher incidence in paediatric patients relative to adults. In summary, the limited size of the overall paediatric exposure is insufficient to guide safe and effective dosing of IONSYS in patients younger than 18 years of age.

Elderly population

Elderly patients (≥ 65 years) made up 28% (499/1763) of the total controlled clinical trial exposure to IONSYS 40 micrograms, with approximately 10% (174/1763) of exposures being in patients ≥ 75 years. No overall differences were observed in the safety of IONSYS fentanyl 40 micrograms in elderly patients (≥ 65 years including a subpopulation ≥ 75 years) and adult patients for all controlled studies. Thus, the adverse reaction profile does not suggest a meaningful difference in safety compared to patients younger than 65 years of age.

Obese patients

In the controlled clinical trial population, the adverse reaction profile in patients with BMI > 40 (86/1436 or 6%) showed no meaningful difference relative to patients with BMI ≤ 40. However, caution is recommended in these patients (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

Symptoms

The manifestations of fentanyl overdose are an extension of its pharmacologic actions, the most serious effect being respiratory depression (see section 5.2).

Treatment

For management of respiratory depression, immediate countermeasures include removing the IONSYS system and physically or verbally stimulating the patient. These actions can be followed by administration of a specific opioid antagonist such as naloxone, based on the clinical judgment of the treating health care professional. Respiratory depression following an overdose may outlast the duration of action of the opioid antagonist. The half-life of the antagonist may be short; therefore, repeated administration or infusion of the antagonist may be necessary. Reversal of the narcotic effect may also result in acute onset of pain and release of catecholamines.

If the clinical situation warrants, a patent airway should be established and maintained, possibly with an oropharyngeal airway or endotracheal tube. Oxygen should be administered and respiration assisted or controlled, as appropriate. Adequate body temperature and fluid intake should also be maintained.

If severe or persistent hypotension occurs, hypovolaemia should be considered and the condition should be managed with appropriate parenteral fluid therapy or other interventions as needed, based upon the clinical judgment of the treating health care professional.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics; phenylpiperidine derivatives; ATC code: N02AB03.

Mechanism of action

Fentanyl is an opioid analgesic, interacting predominantly with the opioid μ-receptor.

Pharmacodynamic effects

Its primary therapeutic actions are analgesia and sedation. Its secondary pharmacological effects are respiratory depression, bradycardia, hypothermia, constipation, miosis, physical dependence and euphoria (see section 5.2).

Clinical efficacy and safety

The efficacy and safety of IONSYS for treatment of acute, moderate to severe postoperative pain was evaluated in seven controlled studies in 1763 IONSYS patients: three placebo-controlled studies and four active-controlled studies. The placebo-controlled trials included 791 patients that were

predominantly female (72%), Caucasian (82%), with a mean age of 45-54 years (range, 18-90 years), and primarily comprised of surgeries including lower abdominal (including pelvic) and orthopedic bone procedures. Patients were enrolled shortly after major surgery if they were not opioid tolerant, were expected to have an uncomplicated recovery, and required at least 24 hours of parenteral opioid treatment. Long-lasting or any non-opioid analgesics were not permitted. Patients were initially titrated to comfort with intravenous fentanyl or morphine, at which point they were randomized to IONSYS or a matching placebo system. During the first 3 hours post-enrollment, patients could supplement with bolus intravenous fentanyl given, as needed, to achieve comfort. After this point 727 patients remained in the studies using only the IONSYS or control system, and were evaluated for efficacy.
The primary endpoint in each placebo-controlled study was the proportion of withdrawals due to inadequate analgesia during the period from 3 to 24-hours after IONSYS application. As illustrated in Table 1 below, IONSYS (fentanyl hydrochloride) was superior to placebo in all studies. Additional analyses suggest that the surgical procedure type did not influence the trends in efficacy endpoints and the efficacy of IONSYS was similar across the range of body mass indices studied (< 25 to ≥ 40 kg/m^2 Body Mass Index).

Table 1: Placebo-controlled Trials (N=727) Patients

Percent (n) of patients who withdrew due to inadequate analgesia Hours 3-24			
Study	**IONSYS n=454**	**Placebo n=273**	**p-value**
C-2001-011	27 % (64/235)	57 % (116/204)	<0.0001
C-2000-008	25 % (36/142)	40 % (19/47)	0.049
C-95-016	8 % (6/77)	41 % (9/22)	0.0001

IONSYS was also evaluated in four active-control trials (predominantly female (65%), Caucasian (85%), with a mean age of 55 years (range, 18-91 years), and primarily comprised of surgeries including lower abdominal and orthopedic bone procedures) using a standard intravenous patient controlled analgesia (PCA) morphine regimen as the comparator. In these studies, 1313 patients undergoing major surgery were randomized to PCA with intravenous morphine (1 mg morphine bolus, 5 minute lock-out, total of 10 mg/h) delivered by a pump, and 1288 patients were randomized to IONSYS. Similar to the placebo-controlled studies, in the immediate postoperative period, patients were titrated to comfort with intravenous fentanyl or morphine per hospital protocol. Once comfortable, patients were then randomized to either IONSYS or intravenous PCA morphine treatment. Patients were instructed to use the system for pain relief.

These studies evaluated IONSYS vs. intravenous PCA morphine in various surgical procedures commonly seen in clinical practice. Study C-2000-007 evaluated patients after undergoing abdominal, thoracic, or orthopedic surgeries; Study CAPSS-319 evaluated patients after undergoing total hip replacement; Study CAPSS-320 assessed IONSYS in patients following abdominal and pelvic surgeries; and Study FEN-PPA-401 assessed patients following major abdominal or orthopedic surgery. Patients could remain in their respective study up to 72 hours if they required parenteral opioid analgesia for this duration. A new IONSYS system was applied every 24 hours to different skin sites, or earlier if all doses were used. Supplemental intravenous opioid medication (fentanyl or morphine) was only allowed during the first 3 hours of IONSYS or PCA morphine treatment. Concomitant use of analgesics was not allowed after 3 hours in Studies C-2000-007 and CAPSS-320. In Study CAPSS-319, half the patients in each group received rofecoxib perioperatively and in Study FEN-PPA-401 patients were allowed non-opioid analgesics throughout the study period. The primary efficacy endpoint was the patient global assessment of method of pain control at 24 hours used to test equivalence between IONSYS and intravenous PCA morphine using a pre-specified ± 10% equivalence boundary with a 2-sided 95% confidence interval. Each patient and investigator was asked to rate the patient's method of pain control as either poor, fair, good, or excellent. Efficacy results at the end of 24 hours, are presented in Table 2 below for the evaluable patient population. As shown below, the primary endpoint, proportion of patients reporting "Good or Excellent" ratings for the two

methods of pain relief in all four studies demonstrated equivalence, with each 95% confidence interval contained within the prespecified ± 10% equivalence boundaries.

Table 2
Active Comparator Trials (n=2569) Evaluable Patients

Study No.	IONSYS (fentanyl) n=1271	IV-PCA (morphine) n=1298	95% CI[a, b]
Patient Global Assessment of Method of Pain Control -1st 24 hour (% of patients rating good or excellent)			
C-2000-007	75% (232/310)	78% (246/316)	(-9.7%, 3.7%)[a, b]
CAPSS-319	84% (326/389)	83% (331/397)	(-4.7%, 5.6%)[a, b]
CAPSS-320	86% (214/250)	85% (212/251)	(-5.1%, 7.4%)[a, b]
FEN-PPA-401	87% (279/322)	88% (293/334)	(-6.2%, 4.0%)[a, b]

[a] 95% Confidence Interval for difference in proportions
[b] The pre-specified equivalence boundary was ± 10%

Across the active-controlled studies, dosing with IONSYS was similar to intravenous PCA morphine pump use. The mean amount of supplemental opioid used during this time was also similar among patients treated with IONSYS or PCA morphine i.e. a range across the 4 studies of a mean dose of 5.0 – 7.5 mg morphine in patients treated with IONSYS compared to a mean dose of 5.4 – 7.7mg morphine in patients receiving PCA morphine. . Patients who completed 24 hours of IONSYS treatment in the seven controlled studies used a wide range of the available 80 doses, with a mean of 29.0 doses/patient (range of 0-93 doses) with the majority of patients (56.5%) using between 11 to 50 doses. A single IONSYS system provided a sufficient number of doses for 99% of the studied patients over 24 hours.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with IONSYS in one or more subsets of the paediatric population for the treatment of acute pain. See section 4.2 for information on paediatric use.

5.2 Pharmacokinetic properties

Absorption

At the initiation of each dose, an electrical current moves a pre-determined amount of fentanyl from the active substance-containing reservoir through the skin and into systemic circulation. IONSYS delivers a nominal dose of 40 micrograms fentanyl over each 10-minute dosing period at steady state. The mean systemic bioavailability is 87%. Upon system removal after the last dose, the decline in serum fentanyl concentration is similar to that of intravenous fentanyl.

Absorption of fentanyl from IONSYS is similar whether applied to the upper outer arm or chest. When the system is applied on the lower inner arm, the amount of fentanyl absorbed is approximately 20% lower than at the upper outer arm or chest. Fentanyl pharmacokinetics are similar with both single and multiple 24 hour applications.

Systemic absorption of fentanyl increases as a function of time independent of the frequency of dosing, with the initial dose being approximately 16 micrograms. Steady state absorption of the nominal 40 microgram dose is achieved about 12 hours after application, indicating that the skin becomes more permeable to fentanyl during the first 12 hours. The pharmacokinetic absorption profile will repeat with each application to a new skin site, therefore with each new application,

absorption will be lower initially. Consequently, the patient may activate IONSYS more frequently to maintain fentanyl blood levels.

When IONSYS is applied without activating the electrical current, the average absorption rate of fentanyl over 24 hours was 2.3 micrograms fentanyl/hour, indicating minimal passive delivery.

Average serum concentrations observed in post-surgical patients were in the range of 0.4-1.5 ng/ml over a 24 hour dosing period. In general, the maximum serum fentanyl concentration occurs approximately 15 minutes after the initiation of a dose.

Following an on-demand dose of fentanyl by IONSYS, fentanyl has an absorption half-life of approximately 15 minutes.

Distribution

Fentanyl is highly lipophilic and is well distributed beyond the vascular system, with a large apparent volume of distribution. Fentanyl exhibits three compartment distribution pharmacokinetics. With intravenous administration, the initial distribution half-life is approximately 6 minutes; the second distribution half-life is 1 hour, and the terminal half-life is 13 hours. The plasma protein binding of fentanyl is 80% to 85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The free fraction of fentanyl increases with acidosis.

The average volume of distribution for fentanyl at steady state is 6 L/kg, the average clearance is 53 L/h.

Biotransformation

Fentanyl is metabolised primarily in the liver to norfentanyl by CYP3A4 isoform. Norfentanyl is not pharmacologically active in animal studies. More than 90% of the administered dose of fentanyl is eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Skin does not appear to metabolise fentanyl delivered transdermally.

Elimination

Around 75% of fentanyl is excreted into the urine, mostly as metabolites, with less than 10% as unchanged active substance. About 9% of the dose is recovered in the faeces, primarily as metabolites. The total plasma clearance of fentanyl following intravenous administration is approximately 42 L/h

Linearity/non-linearity

Dose proportionality has been demonstrated from 25 to 60 micrograms per dose.
None of the four demographic factors studied [weight (lean/obese), age, race, or gender] had a significant effect on active substance exposure (AUC) following use of IONSYS.

Pharmacokinetic /pharmacodynamic relationship

Minimum effective analgesic serum concentrations of fentanyl in opioid-naïve patients treated for acute post-operative pain range from 0.2 to 1.2 ng/ml; undesirable effects increase in frequency at serum levels above 2 ng/ml.

Patients with genetic polymorphisms affecting CYP3A4 and CYP3A5

Published literature has indicated that the CYP3A4*22 and CYP3A5*3 single nucleotide polymorphisms influence fentanyl to norfentanyl metabolism with the potential for increased fentanyl exposure in patients with these genetic polymorphs. Literature has shown that the genetic polymorphisms only account for a small amount of variability in concentrations of fentanyl with

transdermal administration. Another published article of 52 elderly Japanese post-operative patients receiving continuous intravenous (IV) fentanyl infusion (0.5-1.5 µg/kg/h) showed increased fentanyl exposure in the CYP3A5*3 group (3*/3*) than in the 1* carrier group. Clinical relevance is unknown from these published articles; however, caution should be used if administering IONSYS in patients with genetic polymorphisms of CYP3A4 and CYP3A5 (see section 4.4).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity.

Standard reproductive and developmental toxicity studies have been carried out using parenteral administration of fentanyl. In a rat study fentanyl did not influence male fertility. Studies with female rats revealed reduced fertility and enhanced embryo mortality.
Effects on the embryo were due to maternal toxicity and not to direct effects of the substance on the developing embryo. There was no indication of teratogenic effects in studies in two species (rats and rabbits). In a study on pre- and postnatal development the survival rate of offspring was significantly reduced at doses which slightly reduced maternal weight. This effect could either be due to altered maternal care or a direct effect of fentanyl on the pups. Effects on somatic development and behaviour of the offspring were not observed.

Mutagenicity testing in bacteria and in rodents yielded negative results. Fentanyl induced mutagenic effects in mammalian cells in vitro, comparable to other opioid analgesics. A mutagenic risk for the use of therapeutic doses seems unlikely since effects appeared only at high concentrations.

A carcinogenicity study (daily subcutaneous injections of fentanyl hydrochloride for two years in Sprague Dawley rats) did not induce any findings indicative of oncogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Bottom housing assembly:
- *bottom housing unit:* glycol-modified polyethylene terephthalate
- *anode hydrogel:* polacrilin, purified water, sodium hydroxide, polyvinyl alcohol
- *cathode hydrogel:* purified water, sodium chloride, sodium citrate, polyvinyl alcohol, anhydrous citric acid, cetylpyridinium chloride
- *anode electrode*: layers of silver foil and electrically conductive adhesive tape
- *cathode electrode*: layers of polyisobutylene/silver chloride/carbon black composite material, silver foil, and electrically conductive adhesive tape
- *skin adhesive*: polybutene, polyisobutylene, and rosin ester
- *protective liner:* polyester film coated on one side with silicone.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years
Use immediately after opening.

6.4 Special precautions for storage

Do not store above 25°C.

Do not refrigerate or freeze.

6.5 Nature and contents of container

Each IONSYS system is packaged in a sealed thermoform tray. The tray contains one Controller and one sachet containing a Drug Unit. The sachet foil is comprised of a lamination of nylon, aluminium foil and a heat seal layer of a copolymer of polyethylene and polymethacrylic acid.

Each tray is packaged in a folding cardboard carton. There are 6 systems per carton.

6.6 Special precautions for disposal and other handling

Contact with the hydrogel can be harmful to humans. If the fentanyl hydrogel contacts the skin during application or removal, the area should be washed with copious amounts of water. Soap, alcohol, or other solvents should not be used to remove the hydrogel because they may enhance the active substances' ability to penetrate the skin.

Disposal

The used IONSYS system contains a dangerous amount of fentanyl within the red hydrogel housing. Gloves must be worn when removing IONSYS from the patient's skin and during disposal. The used system should be handled carefully by the sides and top. Contact with the hydrogel should be avoided.

The design of the system allows separate disposal of the hydrogel housing and the Controller.

To dispose of a used IONSYS system:

1. Hold the Controller in one hand and pull the red tab with the other hand to separate the hydrogel housing from the system.

2. Fold the hydrogel housing in half with the sticky side facing in.

3. Dispose of the folded hydrogel housing in accordance with local requirements for opioid medicinal products.

4. Dispose of remainder of the system, containing electronics, according to hospital procedures for battery waste.

Local arrangements should be in place to ensure that used systems are returned appropriately (e.g., to hospital pharmacies) for disposal of the residual fentanyl in the hydrogel. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Incline Therapeutics Europe Ltd
21 St. Thomas Street
Bristol
BS1 6JS
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1050/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 November 2015.

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.