# SCIENTIFIC DISCUSSION

## 1.1 Introduction

The IONSYS (fentanyl HCl) system 40 µg is a noninvasive, self-contained, preprogrammed, patient-controlled analgesia (PCA) system that is applied to the upper arm or chest. It is a novel, electrically assisted transdermal delivery system designed for the management of acute pain in patients requiring opioid anagesia and has been developed as a needle-free alternative to current modes of PCA for acute pain.

The scientific rationale for IONSYS (fentanyl HCl) is grounded in the clinical utility of fentanyl PCA and iontophoresis. The standard of care for the management of acute post-operative pain is intravenous PCA. Studies have demonstrated that fentanyl can be delivered transdermally by iontophoresis, providing a means of relatively rapid, on-demand, patient-controlled, noninvasive drug delivery.

The IONSYS (fentanyl HCl) system is designed to provide 24-hour preprogrammed, disposable, noninvasive, delivery of fentanyl with a sufficient number of on-demand doses to allow the majority of patients to achieve safe and effective analgesia without the need for i.v. PCA.

IONSYS™ (fentanyl HCl) system is a needle-free, patient-controlled transdermal analgesic (PCTA) system for on-demand dosing, delivering a nominal 40 µg fentanyl per on-demand dose over a ten minute dose duration. The maximum dosage for each system is 240 µg (6 doses) per hour and 80 doses of 40µg in a 24-hour period. This is equivalent to 3.2 mg/day.

The IONSYS (fentanyl HCl) system uses iontophoresis to deliver fentanyl transdermally, by means of an electric current. The device incorporates a number of safety features to ensure safe usage. The dose initiation button is recessed and requires two presses within three seconds in order to prevent inadvertent dose activation. The system uses an audible tone and an LED to signify dose initiation. The LED remains on for the duration of the 10 minute dosing period. The system also incorporates error detection systems that notify the user/healthcare worker of device problems.

Fentanyl is a synthetic opioid related to the phenylpiperidine class of compounds. It is a highly sensitive µ-receptor agonist and is about 100 times more potent than morphine as an analgesic. Opioids exert their therapeutic effects by mimicking the action of endogenous opioid peptides at opioid receptors. Effects on both local neurons and intrinsic pain modulating circuitry lead to analgesia and other therapeutic effects as well as undesirable side effects, the most serious of which is respiratory depression.
The proposed indication is for "the management of acute moderate to severe post-operative pain in a medically supervised setting."

The Applicant sought CPMP Scientific Advice regarding the development of IONSYS. The Scientific Advice letter was adopted by CPMP in February 1999 (CPMP/349/99At the time of the clinical development, the current CPMP Note for Guidance on Clinical Investigation of Medicinal Products for Treatment of Noniceptive Pain was not available (CPMP/EWP/612/00, date for coming into operation May 2003). The applicant presents four pivotal efficacy studies. Three placebo controlled studies and one active control, non-inferiority study versus i.v. PCA morphine.

## 1.2 Quality aspects

Composition

Ionsys is a needle-free, patient-controlled transdermal analgesic system used for on-demand dosing by the patient. The active substance is fentanyl. Ionsys uses iontophoresis to deliver fentanyl transdermally . Each patch contains 10.8 mg fentanyl hydrochloride and is delivering 40 µg fentanyl per on-demand dose over a ten-minute dose duration. The maximum dose for each system is 240 µg (6 doses) per hour and 80 doses of 40µg in a 24-hour period equivalent to 3.2 mg/day.

Ionsys consists of a top housing assembly (device component) and a bottom housing assembly (drug component). The top housing assembly is composed of an injection-molded plastic component () that protects the electronics and a printed circuit board assembly (PCBA).Audible tones and LED are used to indicate dose delivery, duration, number of doses and also to alert the patient to problems with the system.

The bottom housing assembly consists of a thermoformed unit containing electrodes and active substance in gels which include a solvent, a matrix polymer, buffering agents and an antimicrobial agent.

A release liner (siliconized polyester film) covers the skin adhesive and both hydrogel formulations and is removed before use. Each iontophoretic transdermal system is packed in a heat sealed sachet.

Active substance

The chemical name of fentanyl hydrochloride is N-phenyl-N-[1-(2 phenylethyl)-4-piperidinyl]-, monohydrochloride. It is a white to off-white solid, soluble in water and methanol. Fentanyl HCl is derived through formation of fentanyl base, for which the active substance manufacturer holds a certificate of suitability. The applicant has submitted an ASMF that provides with details on the manufacturing process of the active substance, the control of materials and process validation.

There are four impurities that might arise from the route of synthesis, one possible degradation product and five other impurities. The specifications for related substances are in line with the pharmacopoeial limits. Where impurities are not described in the Ph. Eur. monograph for fentanyl, they are controlled at the qualification threshold of 0.15 % in accordance with the ICH guidelines. The limits of the residual solvents used for the manufacture of the active are also in accordance with the ICH guidelines.

Active substance specification

The specification of the active substance includes tests for description, identification loss on drying , impurities heavy metals , residual solvents chloride , water and residue on ignition .

Batch analysis data have been provided for three batches and in all cases the analytical results complied with the proposed specification.

**Stability**

Stability studies have been performed on batches of the active substance in accordance with ICH guidelines. Samples were stored at 25 $^{o}$C/ 60% RH for 36 months. The analytical methods used were the same as those used for the release and were stability indicating.

All parameters evaluated comply with the active substance specification. The stability data presented support the proposed re-test period for fentanyl HCl when stored in the proposed packaging and storage conditions.

Other ingredients

. All materials are of non-animal origin. For non-pharmacopoeial excipients detailed data on the manufacturing process, impurities, stability and shelf life have been provided. The rest of the materials comply with Ph. Eur. requirements.

**Product development and finished product**

The purpose of the product development was to design a safe, non-invasive and convenient alternative to conventional intravenous (iv) patient-controlled analgesia (PCA) by using iontophoresis-based transdermal delivery of fentanyl through intact skin.

The critical factors affecting the pharmacokinetic and therapeutic performance of the system are the anode hydrogel formulation and the device electrical output parameters. Based on Faraday's law the two important anode formulation parameters that affect the rate of transdermal fentanyl delivery are (1) the drug content (which influences the drug concentration in the skin) and (2) the pH (influences

the fentanyl HCl solubility). These parameters together with the current output of the system and the duration of the dosing period determine the amount of fentanyl delivered during each activation of the system by the patient. The dependence of the amount of fentanyl delivered on charge (product of current and duration) has been confirmed by in vivo human studies and in vitro. Furthermore, an IVIVC has been established using data from clinical study and in vitro data.

The manufacturing of the finished product is composed of the following five steps: (1) / hydrogel mixing, (2) Preparation of bottom housing assembly, (3) Freeze curing bottom housing assembly, (4) Final assembly, and (5) Packaging. All manufacturing stages and in-process controls have been described in detail. The process has been adequately validated according to ICH requirements and data from nine full-scale commercial validation batches have been provided.

The anode and cathode formulations intended for marketing have been used in all pivotal pharmacokinetic, safety and efficacy trials.

**Product specification**

A novel test apparatus known as the System Functionality Test Apparatus (SFTA) and method have been developed for testing the drug release, system functionality and the electrical circuit function.

The product specifications include tests by validated methods for the appearance, content uniformity, assay, identification, impurities cetylpyridinium chloride , drug release, adhesion to steel and release liner peel, number of doses delivered, pH, dose amount, microbiological purity , electronic function test, interdose current. The specification and control tests applied for the finished product at time of release and throughout the life of the product are in compliance with pharmacopoeial standards and ICH guidelines. The limits for each specification test are supported by stability data.

Batch analysis data from production scale batches of the finished product have been provided. All batches met the test limits as defined in the release specification and test methodology valid at the time of batch release and indicated that patches of consistent quality are obtained.

**Stability of the product**

Stability studies have been performed on batches of Ionsys using a different switch that the one intended for marketing. The samples were stored for up to 24 months at 25°C/60%RH 30°C/20%RH, 40°C/15%RH and 40°C/75%RH. Additional stability data have been provided from 3 stability batches, which incorporated device reliability enhancements. The later have been stored up to 6 months at 25°C/60%RH, 30°C/65%RH and 40°C/75%RH.

Stability studies of the system as intended for marketing have been performed with proof of concept and validation batches. Samples were stored for up to 9 months at 25°C/60%RH 30°C/65 %RH, 40°C/15%RH and 40°C/75%RH.

All samples were packaged in the packaging intended for marketing.. The analytical methods used for the analysis of stability samples are the same as those used for batch release.

The physical, chemical, and pharmaceutical characteristics studied are shown to be virtually unaffected by the storage time. No significant changes in the characteristics of the finished product were found. The device parameters in the system intended for marketing were also within acceptable ranges for all time periods tested.

In addition the photostability of the unpouched systems was evaluated, and little or no photo degradation was observed.

**Discussion on chemical, pharmaceutical and biological aspects.**

Ionsys is a needle-free, patient-controlled transdermal analgesic system used for on-demand dosing, by the patient. Unlike conventional transdermal patches, where the active substance is delivered to the systemic circulation through passive diffusion for as long as the patch is applied to the skin, Ionsys uses iontophoresis to deliver fentanyl transdermally from a hydrogel formulation by means of an electric current. This means that the dose is not delivered continuously, but only upon demand from the patient. In contrast to conventional transdermal patches Ionsys is composed of a device component and a drug component that contains the active substance in a hydrogel formulation. In general the quality of Ionsys is adequately established. There are no major deviations from EU and ICH

requirements. Issues concerning the device reliability and performance have been addressed satisfactorily. The active substance is well known, stable and well documented. All critical aspects of the development of the transdermal patch formulation have been studied resulting in a manufacturing process that consistently produces patches, which meet the predefined quality criteria. The packaging material are commonly used and well documented. Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

## 1.3 Non-clinical aspects

### Introduction

Fentanyl is a well-known narcotic analgesic drug, which has been authorised in Europe for intravenous (IV) administration since 1963 and for transdermal administration (Durogesic) since 1994. Many of these studies were carried out in the 1960's and 1970's and were therefore not carried out to current GLP standards. Nevertheless, these studies are considered relevant for the safety assessment. The MA applicant has conducted a number of additional toxicity studies according to GLP.

### Pharmacology

Fentanyl was developed by Janssen and the pharmacodynamic activity in animals was extensively evaluated in early studies during the 1960s and 1970s and is well documented in the literature. No additional animal pharmacodynamic studies have therefore been conducted for the current Marketing Authorisation Application.

The finished product, IONSYS (fentanyl HCl) is an integrated system, which uses iontophoresis to introduce fentanyl transdermally from a hydrogel, by means of an electric current, for on-demand dosing by the patient, in the management of acute moderate to severe post-operative pain in a medically supervised setting. Each system contains 10 mg fentanyl hydrochloride. Following application, activation by pressing the button delivers a nominal 40µg fentanyl. The maximum dosage for each system is 80 doses of 40µg in a 24-hour period. This equates to 3.2 mg/day or 60µg/kg/day for a 50 kg person.

- Primary pharmacodynamics (*in vitro/in vivo*)

Fentanyl is a phenylpiperidine analgesic that, depending on the species and the methods used to measure antinociception, is approximately 80 to 290 times more potent than morphine but has a shorter duration of action after a single bolus administration. Antinociceptive effects can be observed after systemic, epidural, intrathecal, and transdermal treatment. The pharmacodynamic effects of fentanyl after transdermal application are identical to those observed following other routes of administration.

Fentanyl, in common with other opioids, binds to opiate receptors and is a potent and relatively selective agonist at these receptors, with a higher binding affinity for µ- as compared to k- or δ-opiate receptors. In receptor binding assays using guinea pig whole brain membrane dissociation constant (Ki) values for fentanyl were 1.2 ± 0.2 nM 180 ± 18 nM and 290 ± 24 nM for µ-, δ- and k- receptors respectively. The effects of fentanyl are readily reversed by opiate-antagonists such as naloxone.

In animals, fentanyl results in antinociceptive effects after i.v., subcutaneous (s.c.), intraperitoneal (i.p.), oral, epidural, intrathecal and transdermal administration.

In rats IV fentanyl is 290 times more potent than morphine, but the duration of action is shorter. Fentanyl's safety margin (LD50/ED50) is 282 compared to 70 for morphine. Data for activity of fentanyl, pethidine and morphine in a rat model is given in the table below.

**Table**: Activity of fentanyl, pethidine and morphine following single intravenous bolus injection in the tail withdrawal reaction test in rats

| Compounds | $ED_{50}$ (mg/kg) | Potency | $LD_{50}$ (mg/kg) | Safety Margin | Peak effect (min) | Duration (min) |
|---|---|---|---|---|---|---|
| Fentanyl | 0.011 | 291.8 | 3.1 | 281.8 | 4 | 30 |
| Pethidine | 6.04 | 0.5 | 29 | 4.8 | 4 | 33 |
| Morphine | 3.21 | 1 | 223 | 69.5 | 30 | 90 |

The pharmacodynamic properties of fentanyl after passive transdermal delivery are identical to those after other routes of administration and have been previously described. Iontophoresis increases transdermal penetration compared to passive diffusion. In an *in vivo* study, transdermal iontophoresis of 40 µg/ml fentanyl for 1 hour to the abdominal skin of hairless rats resulted in an antinociceptive effect in the tail flick test, which lasted approximately 4 hours. The percentage of maximal possible effect reached 31.1% for fentanyl.

- Secondary pharmacodynamics and Safety pharmacology

Fentanyl stimulates the µ-opiate receptor, resulting in specific secondary effects such as respiratory depression, bradycardia, hypothermia, constipation, miosis, physical dependence and euphoria. However, fentanyl was shown to have a relatively high safety margin towards cardiovascular, metabolic and neurological affects. All these effects are well documented in both preclinical and clinical studies. A brief overview of the effects of fentanyl on major organ systems is presented in this section.

Effects on central nervous system

In mice following s.c. injection of 0.01 to 1.0 mg/kg fentanyl citrate, typical opiate effects including increased spontaneous motor activity, Straub tail reaction, increased muscle tone, mydriasis, respiratory depression and convulsions occurred. The intensity and duration of these effects were dose-related. Onset of effects was evident within 1-2 minutes of administration with a duration of 1 hour at 1.0 mg/kg.

In dogs, intramuscular administration of doses varying from 0.0125 to 1.0 mg/kg fentanyl citrate produced similar effects at all dose levels. Within 10 minutes after the administration of fentanyl citrate, decreased motor activity, ataxia, decreased responsiveness to auditory and painful stimuli, bradycardia, respiratory depression, salivation and defecation were observed. The intensity and duration of these effects increased with the dose used.

Nalorphine, administered intravenously at the peak of CNS depression, resulted in an immediate reversal of the central depression induced by fentanyl.

Opiates may produce convulsions, which in general are accompanied by a rise in O2 consumption of the cerebrum followed by exhaustion of the CNS and metabolic acidosis. The frequency and severity of opiate induced convulsions is dose related. In dogs, high i.v. doses of fentanyl (4 mg/kg) produced epileptiform seizure activity in the electroencephalogram (EEG). A comparison of the i.v. doses that produced severe convulsions with those required to obtain deep surgical analgesia indicated a safety margin for neurological toxicity in dogs of 160 for fentanyl and 72 for morphine.

Cardiovascular effects

The cardiovascular effects of fentanyl have been studied extensively. In early studies in dogs, following i.v. administration, fentanyl citrate at doses of 0.0025 to 0.005 mg/kg produced negligible effects on blood pressure, heart rate and electrocardiograms (ECG's) whereas higher doses (0.01 to 0.04 mg/kg) produced hypotension, bradycardia and some ECG changes.

In dogs, an inverse relationship has been described between the cardiovascular toxicity and analgesic potency of opioids. A high dose of 5.0 mg/kg i.v. morphine, necessary for deep surgical anaesthesia, produced a severe tachycardia and vasodilatation with a depression of the myocardial contractility and impairment of the pulmonary circulation. This reaction did not occur after equi-analgesic doses of 0.05 mg/kg i.v. fentanyl. The cardiovascular system remained stable, with the advantage of an increased venous return and myocardial contractility. The safety margin in dogs, expressed as the ratio between the doses producing severe cardiovascular side-effects and doses necessary for deep surgical analgesia, has been reported to be 5 times higher for fentanyl than for morphine.

Respiratory effects

Opiate receptors are found in areas involved in the regulation of respiration such as the medulla. Fentanyl interacts with these receptors and may cause respiratory depression. The degree of respiratory depression observed with opioids depends on various factors, including the opioid used, the plasma concentration reached, the route of administration and the duration of opioid intake since tolerance develops to this effect.

In anaesthetised dogs, fentanyl citrate produced a reduction in respiratory minute volume following i.v. doses of 0.010 to 0.040 mg/kg. Maximal depression occurred 1 minute after injection with marked recovery within 5 minutes. Nalorphine reversed the respiratory depressant effects of fentanyl. Morphine 0.5 to 2.0 mg/kg i.v. caused similar affects.

Van den Hoogen *et al*. evaluated the respiratory effects of fentanyl in rats after s.c. and epidural injection. In rats breathing 8% carbon dioxide, the s.c. dose of fentanyl that reduced minute volume by 25% as compared to control values (ventilation inhibitory dose required to produce a 25% depression in minute volume (ID25)) was 0.030 mg/kg, which is 2.5 times the ED50 for s.c. analgesia (0.012 mg/kg). The ventilation ID25 after epidural administration was 0.056 mg/kg, which was about 18 times greater than the epidural analgesia ED50 of 0.0032 mg/kg. With s.c. morphine or pethidine, the corresponding ratios between respiratory depression and analgesia were 1.6 and 1.7, respectively.

Gastrointestinal effects

Opioids are known to suppress the output of faecal pellets in mice. At equianalgesic doses administered subcutaneously, fentanyl (0.09 to 1.6 mg/kg) had a less pronounced constipating effect than morphine (12 to 240 mg/kg).

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Following s.c. administration, the ED50 for fentanyl citrate in the castor oil diarrhoea test was 0.028 mg/kg compared to 0.22 mg/kg for morphine. The dissociation factor between the analgesic and anti-diarrhoeal effect was much smaller (1.1) for fentanyl than for morphine (36).

Fentanyl has been demonstrated to produce less nausea and vomiting than morphine in animals. For example, in a crossover study in mongrel dogs, doses of 1.0 and 2.50 mg/kg fentanyl citrate given intramuscularly, were devoid of emetic activity. Following the same doses of morphine, emesis was generally observed within 15 minutes in 60% to 90 % of the dogs.

Metabolic effects

The effects of high i.v. doses of fentanyl and other opiates on a range of metabolic parameters were investigated in dogs. Fentanyl at i.v. doses up to 0.32 mg/kg did not produce metabolic acidosis and hypermetabolism but on the contrary produced metabolic stimulation. In contrast, morphine at doses from 20 mg/kg administered intravenously produced marked acidosis and an important rise in total O2 consumption. Rises in blood catecholamine levels and other biochemical and metabolic changes were observed following high i.v. doses of fentanyl 0.05 to 4 mg/kg and morphine 5 to 200 mg/kg.

Based on the findings in these investigations, the safety margins for metabolic toxicity, calculated as the ratio between the doses producing severe metabolic side-effects such as acidosis and hyper metabolism, and those needed for deep surgical analgesia, were 60 for fentanyl and 13 for morphine.

Abuse potential, withdrawal and tolerance

Fentanyl, like other opioids, has intrinsic discriminative stimulus properties in various species, indicating a potential for abuse. Fentanyl also suppresses the withdrawal symptoms of morphine-addicted monkeys at about 1/75th of the morphine dose.

Tolerance to the antinociceptive effects of opioids after systemic administration has been reported to develop. However, the degree of tolerance after s.c. administration was less with fentanyl as compared to morphine in rats.

Pharmacodynamics of metabolites

Fentanyl is rapidly and extensively metabolised in the liver of animal species and man. The oxidative *N*-dealkylation at the piperidine nitrogen, yielding phenylacetic acid and norfentanyl, appears to be the main metabolic pathway. In addition, metabolites are formed via aromatic and aliphatic hydroxylations.

Two minor hydroxylated metabolites, α-hydroxy-fentanyl and para-hydroxy-fentanyl (or: 4-hydroxy-phenethyl-fentanyl) show some activity in the guinea-pig ileum bioassay. In the rat, these metabolites were recovered from brain tissue, but in small amounts relative to unchanged fentanyl.

In general, the metabolites of fentanyl do not contribute to the analgesic activity, as demonstrated by their weak activity in the guinea-pig ileum bioassay and the two *in vivo* assays, the hot plate test in mice and the tail withdrawal test in rats

- Pharmacodynamic drug interactions

The concomitant use of CNS depressants, including other opioids, sedatives or hypnotics, general anaesthetics, phenothiazines, tranquillisers, skeletal muscle relaxants, sedating antihistamines, and alcoholic beverages may produce additive depressant effects. Hypoventilation, hypotension and profound sedation or coma may occur.

**Pharmacokinetics**

The pharmacokinetics of fentanyl following parenteral and transdermal (patch) administration are well characterised.

- Absorption- Bioavailability

In in vitro experiments using viable rat skin, iontophoresis enhanced fentanyl penetration by a factor 10 to 40 compared to passive diffusion, and skin penetration increased with prolonged duration of iontophoresis.

It appears that the formation of a skin reservoir of fentanyl during iontophoresis is an important determinant of the pharmacokinetic of iontophoretically applied fentanyl. The slow decrease of fentanyl plasma levels, after the iontophoresis current was stopped, was ascribed in in vivo studies in rats to both continuing release of fentanyl from a built-up skin reservoir and redistribution of fentanyl from peripheral compartments.

A number of variables were found to affect fentanyl skin penetration. Fentanyl flux through the skin was increased with increased current density applied (direct or pulsed), with increased current application, with lower pH in the donor compartment, and with increased fentanyl citrate concentration in the donor compartment. At the same current density, direct current induced a somewhat higher flux than pulsed current.

- Distribution

Distribution of fentanyl has been examined in mice, rats, guinea pigs, rabbits, dogs and sheep. In all animal species studied, the fast onset as well as the short duration of the effect of fentanyl after

intravenous administration were ascribed to the very pronounced and rapid uptake of the drug in brain followed by a rapid redistribution to sites of storage (muscle and fat) and biotransformation (liver).

- Metabolism (*in vitro/in vivo*)

The main metabolic pathway of fentanyl in animals and man is the oxidative N-dealkylation to norfentanyl, with the possible exception of the dog. In addition, metabolites are formed via aromatic as well as aliphatic hydroxylation. Amide hydrolysis appears to be a minor pathway or does not occur at all. The narcotic analgesic activity of fentanyl can be ascribed to unchanged drug.

CYP3A4 is the major human P450 isoform involved in the main fentanyl metabolic route, the oxidative N-dealkylation to norfentanyl. These metabolites are devoid of analgesic activity. This major route of metabolism predisposes to clinically significant pharmacokinetic drug-drug interactions. Fentanyl is an inhibitor of CYP3A4 in human liver microsomes, but the Km is considerably higher than plasma fentanyl concentrations attained during proposed clinical use of IONSYS. In contrast, coadministration of potent CYP3A4 inhibitors, most notably HIV-protease inhibitors and ketoconazole, may result in clinically relevant inhibition of fentanyl clearance and these combinations are best avoided.

- Excretion

Based on the low urinary recovery of unchanged fentanyl after intravenous or intramuscular administration, renal clearance of fentanyl is low in rats, dogs and man.Fentanyl metabolites formed are eliminated both in urine and in faeces.

**Toxicology**

- Single dose toxicity

The majority of the single dose toxicity studies were conducted in the 1960s and 1970s, whereby fentanyl was tested in mice, rats, dogs, hamsters, guinea-pigs, monkeys and cats, following oral, intravenous (i.v.), intramuscular (i.m.), subcutaneous (s.c), intra-arterial (i.a.) and intragastric (i.g.) administration. As expected, decreased activity or decreased activity followed by increased activity were observed in rodents, and convulsions, tremors, loss of righting reflex, sedation and respiratory depression in dogs. Detailed summaries have not been provided for these studies as they have previously been used in support of other fentanyl applications and were not carried out according to current GLP standards. In view of the well-known properties of fentanyl and its long-established clinical use, no further toxicity studies with the active subtance are necessary.

- Repeat dose toxicity (with toxicokinetics)

In a 4-week i.v.GLP repeated dose toxicity study in rats, macroscopic and histological examination did not reveal any treatment-related effects. Fentanyl was well tolerated and did not result in any adverse effects when dosed at 0.025 mg/kg. When rats were dosed at 0.1 mg/kg, a few females became slightly excited in the last week of dosing. In addition, slight increases in serum glucose in both sexes and in serum inorganic phosphate in females were present. At a dose of 0.4 mg/kg, excitation was seen in several males and females. Decreases in food consumption, especially in males, as well as slight changes in some serum parameters were present in both sexes (increases in calcium and glucose in both sexes and increases in potassium and inorganic phosphate in females). In males, a slight decrease in body weight towards the end of the dosing period and a pronounced decrease in the first week of the recovery period were present, resulting in a slight decrease in the weight of the liver. All changes were reversible within a four-week recovery period. The results of the non-GLP studies (parenteral administration) in rats were comparable.

The results of the studies performed using a commercially available fentanyl patch in rabbits indicated that this transdermal formulation of fentanyl produced no evidence of systemic toxicity and only a mild degree of irritancy.

In dogs, two 4-week parenteral toxicity studies gave slightly variable results.All the animals receiving fentanyl were sedated immediately after the administration of the compound, resulting in occasional

hyperpnoea, decreased food intake and lack of defecation. Upon recovery from sedation, excitement was occasionally observed in the dogs. Convulsions were seen in all dosage groups. These effects, sedation as well as convulsions, were much more pronounced at the highest dose (1 mg/kg i.v.) than in the 0.1 and 0.3 mg/kg i.v. dosage groups. In addition, emesis and loss of righting reflex were observed in the animals of the 1 mg/kg dosage group. Histological changes in the liver and the kidneys were related to the test article, and were generally observed at the highest dose level (1 mg/kg). In the second 4-week study, a dose of 0.4 mg/kg i.m.did not result in histological changes.

No sub-chronic studies for systemic toxicity potential have been performed on IONSYS (fentanyl HCl), but dermal irritancy potential and contact sensitisation potential have been studied.

The results of the repeated dose toxicity studies using parenteral administration are relevant to this application, since iontophoresis increases the availability of fentanyl. The results of toxicology studies using fentanyl patch are less relevant in this context, since the local tolerance is expected to be different when using iontophoresis to aid transdermal delivery.

- Genotoxicity in vitro and in vivo (with toxicokinetics)

The in vitro forward mutation tests of the mouse lymphoma TK locus gave altogether conflicting and inconclusive results. However, the rest of the in vitro tests, including Ames test, unscheduled DNA synthesis test and mammalian cell transformation test gave negative results. The in vitro and in vivo chromosomal aberration tests gave negative results. Altogether, it is concluded that the intended clinical use of the product is not considered to be associated with mutagenic/clastogenic risk.

- Carcinogenicity (with toxicokinetics)

The decision not to carry out carcinogenicity studies with fentanyl for the intended short-term clinical use of IONSYS is acceptable. However a carcinogenicity study with the fentanyl transdermal formulation (which is indicated for longer term use) is under way.

- Reproductive and developmental studies

Standard reproductive and developmental toxicity studies have been carried out using parenteral administration of fentanyl.
It can be concluded that fentanyl, when dosed up to 0.4 mg/kg/day as continuous i.v. infusion, had no adverse effects on the fertility of male or female rats and that embryo-foetal development was not adversely affected.
Fentanyl up to 0.4 mg/kg/day as continuous i.v. infusion had no effects on the fertility of female rabbits and the embryo-foetal development was not adversely affected. No teratogenic effect was observed.
Fentanyl was not teratogenic when administered intravenously to rats at dosages of 0.01 or 0.03 mg/kg/day during the period of organogenesis, or subcutaneously at doses up to 1.25 mg/kg/day.
Fentanyl did not result in primary effects on peri-and postnatal parameters on the F1-generation and it is not considered to be a behavioural teratogen in rats at doses up to 0.4 mg/kg.

- Local tolerance

*Irritation potential*
The non-clinical safety programme for IONSYS (fentanyl HCl) was designed to evaluate the local dermal irritation and sensitisation potential of the modified release pattern of fentanyl. Several studies were conducted in guinea pigs to evaluate the sensitisation potential of constituents of the IONSYS (fentanyl HCl) hydrogels and the adhesive.

Local tolerance has been studied with single and repeated administration of IONSYS and using different anode and cathode hydrogel formulations and current densities.

Increased current density was found to be associated with increasing irritation. Repeated administration also appeared to result in higher irritation scores, although this was not not consistently

observed, and irritation continued to be present for at least 48 hours after repeated administration. In clinical use, IONSYS may be administered for up to three 24-hour periods. The clinical use of the product is also different from the nonclinical studies in that patients will determine the frequency of dosing, and hence also electric current delivery.

In a repeated administration study in hairless guinea pigs, the skin irritation scores categorised both the cathode and anode mild to moderate irritants. The observations made post 48 hours to determine the resolution of the irritated skin sites showed mild irritation for the cathode and mild to low moderate irritation for the anode. In general, as the number of applications increased from one to four, there was no increase in irritation at the anode and cathode sites in this study. There was also no consistent decrease in irritation as the number of days between applications increased.

Histological assessment of those sites treated with ETS containing saline hydrogels revealed biologically meaningful increases in incidence and severity of dermatitis (lymphohistiocytic (LHC) and polymorphonuclear (PMN) cellular infiltrates), parakeratosis, acanthosis, hyperkeratosis, inflammatory crusts (serocellular crusts), and epidermal necrosis (ulceration), when compared to the respective untreated control sites. LHC cellular infiltrates, acanthosis, and hyperkeratosis by incidence were the three major changes or lesions that were observed in 100% of the animals in nine of the eleven groups of cathode and anode treatment sites.

Comparing different cathode treatment sites, LHC cellular infiltrates, hyperkeratosis, acanthosis, and parakeratosis were unrelated to the number of applications (increased applications did not consistently result in increased severity). An increase of LHC cellular infiltrates and parakeratosis appeared to be related to an increase in current density but this was not apparent for hyperkeratosis and acanthosis. When comparing different anode treatment sites only parakeratosis appeared to be related to an increase in current density. For both the cathode and anode, the incidence and severity of the PMN cellular infiltrates and serocellular crusts could not be attributed to any particular dosing schedule or current density, although it was obviously related to treatment. Histopathologically, the anode sites were slightly more irritated or inflamed than the cathode sites. All the skin lesions ranged from minimal to marked in severity.

The cathode hydrogel containing 0.08% CPC and the cathode hydrogel containing 0.2% CPC (corresponding to the formulation intended for marketing) were mild irritants in guinea pigs and rabbits. The corresponding anode was a mild irritant in guinea pigs and a non- to negligible irritant in rabbits. The MA24 adhesive was a mild irritant in guinea pigs and a moderate irritant in rabbits. The adhesive was a mild irritant in guinea pigs and a moderate irritant in rabbits.

These results suggest that there is some potential for IONSYS (fentanyl HCl) to cause irritation in particular the presence of CPC as a bactericidal agent in the cathode hydrogel and the presence of polacrilin in the anode hydrogel was questioned by the CHMP in view of their irritant properties. However the results show only mild to moderate dermal irritation.

*Sensitisation potential*
No evidence of sensitisation occurred in the animals induced and challenged with the anode placebo hydrogel containing histidine with polacrilin, thereby categorizing it as a weak sensitiser. No evidence of sensitisation occurred in the animals induced and challenged with the cathode hydrogel (at either 0.05 mA/cm2 or 0.03 mA/cm2), thereby categorizing it as a weak sensitiser. However, it should be noted that the hydrogel formulations were not identical to the market-image formulation.

Sensitisation occurred in the animals induced and challenged with the IONSYS (placebo), cetylpyridinium chloride, or extracts of adhesive), categorizing these as weak sensitisers. An intradermal extract of the polacrilin buffer was considered a weak to mild sensitiser. The IONSYS (fentanyl HCl) was categorized as a mild to moderate sensitiser, but the effects were influenced by concurrent irritation. Fentanyl itself has been shown not to be a sensitiser in guinea pigs. No animals induced with Cetylpyridinium chloride (CPC), a bactericidal agent included in the hydrogel, were considered to be sensitised upon intradermal or topical challenge, categorizing CPC as a weak sensitiser under the conditions of this study.

*Biocompatibility*
An *in vitro* cytotoxicity study (TR-98-1561-023) was conducted to confirm biocompatibility, of the ink hardener used in the commercial housing. The test mixture extract and all dilutions of the extract were determined to be noncytotoxic to L-929 cells.

- Other toxicity studies

*Dependence potential*
As a strong opioid, fentanyl has the potential to induce dependence. This has been addressed in the review of pharmacodynamic properties. Since the medicinal product is intended for use in a medically supervised setting and indicated only for the short term management of postoperative pain, there are no specific concerns related to dependence potential of this medicinal product.

**Ecotoxicity/environmental risk assessment**

The applicant has carried out Predicted Environmental Concentration calculations. According to the results, the intended use of the medicinal product is not considered to represent a risk to the aquatic or soil compartment.

On the patient leaflet, instructions are given to dispose of a used IONSYS system as medical waste in accordance with local regulations. The design of the patch allows separate disposal of the red fentanyl-containing bottom housing and the white electronic/battery-containing top housing. Disposal of IONSYS should be done by medical staff only.

**Discussion on the non-clinical aspects**

Non-clinical data generated to support previous applications for fentanyl-containing products have been reviewed.
The pharmacodynamics and safety pharmacology of fentanyl are well characterised.
The non-clinical development programme has appropriately concentrated on studies specifically relating to the new mode of delivery and to the components of the IONSYS system.

The applicant adequately quantified the flux of fentanyl across the skin from the IONSYS unit. There were no unexpected findings.

Results of repeated dose toxicity studies and mutagenicity/clastogenicity tests do not raise specific concern over carcinogenic potential.

Altogether, a comprehensive programme of local tolerance and sensitisation studies have been carried out. The results show a mild to moderate skin irritation and sensitisation potential.

## 1.4 Clinical aspects

**Introduction**

The clinical pharmacology of transdermal fentanyl hydrochloride from IONSYS was investigated in a total of 20 studies. A total of 412 healthy volunteers and 1153 post-operative patients were exposed to IONSYS in these studies. The applicant present results of 10 pharmacokinetic studies in 340 healthy volunteers, 4 pharmacokinetic studies in 1128 patients, one pharmacokinetic study in 25 paediatric patients, and 5 clinical pharmacology supporting studies on 72 healthy volunteers. Studies were design to identify the optimal system, e.g. output current, current density, dose duration and hydrogel formulation, to evaluate passive fentanyl delivery from the IONSYS, the bioavailability of fentanyl hydrochloride, the effects of different application sites of the system, and different dosing regiments, and the effects of different demographic characteristics.

Study designs in most volunteers studies were single-centre, open-label, randomised and crossover designs with 2-4 treatment periods and IV fentanyl citrate performing as a control group. In volunteer studies the subjects were pre-treated with oral naltrexone to block the opioid effect of fentanyl. Most patient studies were multicentre studies.

The clinical efficacy programme with IONSYS (fentanyl HCL) 40 ug system included four pivotal Phase III trials (studies C-2001-011, C-2000-008, C-95-016, C-2000-007). Three trials (studies C-2001-011, C-2000-008, C-95-016) were placebo-controlled studies designed to demonstrate efficacy and safety when used in the control of post-operative pain. Two of these were multicentre trials and one single-centre conducted study. The fourth trial was an open, active-controlled multicentre study using IV morphine PCA as a comparator (study C-2000-007). There were also four uncontrolled trials, in which the safety and efficacy of the 40 µg system was assessed in post-operative setting (C-93-023, C-94-043) after discharge to medically supervised setting post-operatively (C-95-019) and in pediatric patients who experienced inadequate analgesia at the 25 µg dose and were switched to higher dose (C-2000-005). The commercial IONSYS (fentanyl HCl) system was used only in study C-2000-005 in the uncontrolled studies.
The studies were conducted according to the GCP standards, as documented by the ICH, and local requirements.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Even though two strengths were studied in clinical trials, 25 µg and 40 µg, the 40 µg strength is the one subject of this marketing authorisation application.
Acute post-operative pain was the model chosen for these studies because of its demonstrated utility in evaluating the efficacy of treatments for moderate to severe acute pain. Visceral and somatic pain associated with major abdominal, thoracic or orthopaedic surgery is considered an appropriate model for the study of acute moderate to severe pain of limited duration as outlined by the Committee for Proprietary Medicinal Products (CPMP) 2002.

Scientific Advice on Clinical Efficacy was sought on 30 September 1998 ands was given on 25 February 1999. The CPMP gave the following advice: the therapeutic indication should be limited to post-operative pain instead of acute pain, in the placebo controlled studies the primary criterion should be the proportion of patients experiencing treatment failure at three hours, Patient Global Assessment provides an integration of pain control over 24 hours and is an acceptable primary efficacy criterion. For home use indication an extensive clinical development is needed because of the safety issues of the product.

The claimed indication is for "the management of acute moderate to severe post-operative pain in a medically supervised setting".

**Pharmacokinetics**

The proposed commercial device, and anode and cathode hydrogel formulation was used in 4 pharmacokinetic studies (C-2000-007, C-2001-006, C-2001-009, and C-2002-027).

The clinical development programme for IONSYS included some studies with a system delivering 25 µg fentanyl per dose, which is lower than the current application for 40 µg per dose.

The applicant has carried out altogether 10 PK-studies where the primary aim was to evaluate the pharmacokinetic properties of IONSYS. Non-compartmental method was used in most studies to calculate pharmacokinetic parameters after IONSYS fentanyl hydrochloride administration, in few studies one- and two-compartmental models were applied. Nonlinear regression was used for estimation of fentanyl hydrochloride absorption.

Most pharmacokinetic parameters were calculated using non-compartmental or one or two-compartment models, taking into account skin absorption.

In most studies IV fentanyl citrate was used as a control group, and for IV-administration pharmacokinetic calculations a two- or three-compartment model was used.

The sampling frequency (5 to 10 minutes intervals) and duration (up to 24 hours after last demand) were sufficient to give an appropriate figure on pharmacokinetic characteristics of IONSYS fentanyl hydrochloride pharmacokinetics.

- Absorption

Overall absorption and bioavailability of fentanyl hydrochloride from IONSYS system has been thoroughly investigated.
40% of the initial dose is absorbed with full absorption approximately 10 – 12 hours and continuing until the system is removed. However patient activation allows for compensation by increasing frequency of dosing.

Both chest and upper arm application provides a constant fentanyl absorption. As the AUC following upper inner arm application was slightly lower, the inner arm application is not recommended. No significant adverse events were reported in application to the upper outer arm or chest. Passive absorption of fentanyl hydrochloride from IONSYS is minimal. When applied to a previously unused site each subsequent system has similar kinetics to the first system.

The pharmacokinetics of fentanyl hydrochloride was evaluated in the study C-93-023 where the IONSYS 40 µg system was used for the treatment of postoperative pain. The majority of patients had plasma concentrations between 1 and 2 ng/ml over the 24 hours study period, which confirms that plasma concentration greater than 1 ng/ml is required to produce sufficient analgesia after surgery. However, it should be noted that the highest fentanyl individual concentrations in the present studies were >10 ng/ml.

In the study C-2000-007, where the proposed commercial device IONSYS 40 µg system was used for the treatment of postoperative pain, blood samples were collected 5 minutes after IONSYS fentanyl hydrochloride delivery. 21% of patients required rescue medication, and some of them were provided both morphine and fentanyl for rescue analgesic. The mean of fentanyl concentration was 0.5 ng/ml and range between 0.0 and 2.0 ng/ml. In the study C-95-016 developmental phase IONSYS system was used for the treatment of postoperative pain, blood samples were collected 5 minutes after IONSYS fentanyl hydrochloride delivery, the mean of fentanyl concentration was 0.7 ng/ml with a range between 0.12 and 2.4 ng/ml.
In study C-2000-007 in several patients other opioids, morphine, sufentanil or alfentanil, were used to titrate the patients to comfort before commencing IONSYS, and several patients were provided morphine for rescue analgesic during the treatment with IONSYS. This may explain why some patients had fentanyl concentration below the level of quantification and why the mean of plasma fentanyl concentration was low, 0.5 ng/ml, which is lower than the proposed analgesic concentration of 1-2 ng/ml.

The inter-individual variability of fentanyl hydrochloride pharmacokinetics from IONSYS is similar to that of IV fentanyl citrate. The intra-patient variability is approx. 17% which is acceptable.

*Influence of skin changes*

Heat
Application of heat has no effect on the intensity of the applied current, or on the charge and electrophilic mobility of the drug. The system actively adjusts the applied electric field to maintain a constant current of 170 microamps during treatment.
The delivered dose of fentanyl is not expected to be significantly affected by increased body temperature because approximately 95% of the drug is delivered via electro- transport with a much smaller proportion by passive delivery.

Sweat
In cases of extreme sweating a fraction of the output electric current from the device could be carried through sweat across a patient's skin rather than into the body. As a consequence, it is really possible that the delivery of fentanyl will be reduced. Further evaluation will be performed in post-marketing.

*Influence of food*
IONSYS is intended for transdermal use, thus the influence of food on pharmacokinetics of fentanyl hydrochloride is considered negligible.

- Distribution

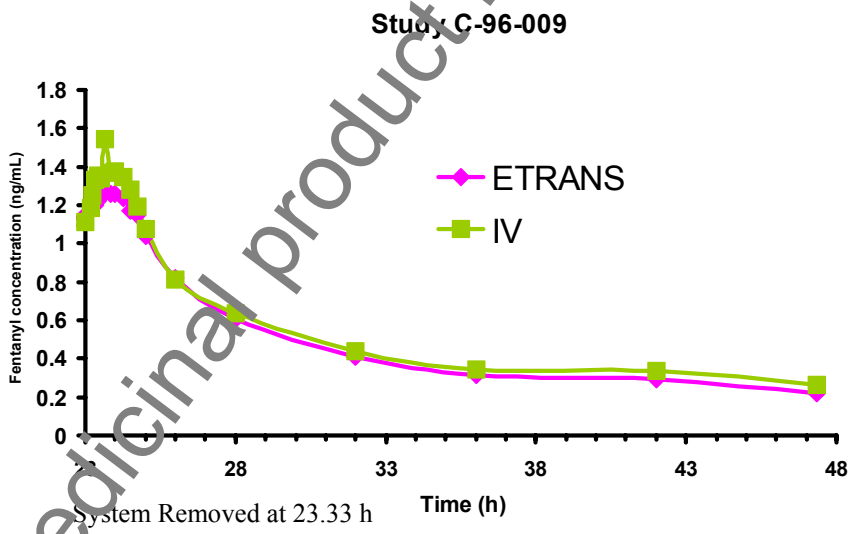
Population pharmacokinetic data analysis show that the clearance of fentanyl was 35 l/h (intersubject CV 69 %) and central volume of distribution 20 l (intersubject CV 266 %), and that mean values are similar to those reported in healthy volunteers. However, it should be noted that half of the patients in the study C-93-023 were provided supplemental analgesic to achieve sufficient analgesic efficacy, up to 50 supplemental doses were required during the 0 to 3 hours, up to 20 doses during the 4 to 6 hours, and the maximum of supplemental analgesic doses during the 24 hours study period was 83 doses, mean (SD) 4 (8) doses.

- Elimination

In man the elimination of fentanyl appears to be triexponential. The initial rapid decline after IV-infusion occurs in 1.4 minutes (rapid tissue uptake), $t_{½\beta}$ is 25 minutes (tissue redistribution), and the terminal plasma elimination half-live is relatively long, 7 to 8 hours.

The total body clearance of fentanyl is high and predominantly metabolic, with the liver being the major site of metabolism. Renal clearance of fentanyl is low, <10%. Fentanyl metabolites are eliminated both in urine and in faeces.

The comparison of fentanyl serum concentration profiles after cessation of IV Infusion and IONSYS™ (ETRANS) treatment is shown in the graphic below:



System Removed at 23.33 h

*Metabolism*
Fentanyl is metabolised into inactive metabolites in the liver. Fentanyl has a high extraction ratio and clearance rates. The main metabolic pathway of fentanyl is N-dealkylation to norfentanyl, and by hydroxylation of both fentanyl and norfentanyl to hydroxypropionyl fentanyl and hydroxypropionyl norfentanyl, respectively. In addition, metabolites are formed via aromatic as well as aliphatic hydroxylation. Based on in vitro data CYP3A4 is the major human P450 isoform involved in the metabolism of fentanyl. Ritonavir and ketoconazole, which are potent CYP3A4 inhibitors, reduces the clearance of fentanyl.

*Interconversion*
Fentanyl is not a chiral product.

*Pharmacokinetics of metabolites*
The pharmacological activity of fentanyl metabolites is believed to be minimal. Fentanyl metabolites undergo further oxidative N-dealkylation and some amide hydrolysis also occurs.

*Excretion*
The renal clearance of fentanyl is low, < 10%. At 72 hours after IV administration, most fentanyl (85%) is recovered as follows: 7% as unchanged drug (6% in urine, 1% in faeces) and 78% as metabolites (70% in urine, 8% in faeces).

- Dose proportionality and time dependencies

Fentanyl plasma concentrations correlates with analgesia (the desired effect) and respiratory depression (the most dangerous side effect). Fentanyl concentrations greater than 1 ng/ml produce slight analgesia and ventilatory depression, those greater than 3 ng/ml yield additional analgesia and a 50% decrease in ventilatory response to carbon dioxide. Concentrations greater than 20 ng/ml cause a loss of consciousness.

Once fentanyl base is absorbed into the epidermis, it is protonated in the systemic circulation to form the fentanyl cation. Therefore the disposition kinetics is expected to be the same for IV and transdermal administrations.

The dose proportionality of the IONSYS system was evaluated in several studies. For study C-96-009 see comment in the section II.1.3, which show that fentanyl hydrochloride absorption increases proportionally with current. In the study C-98-013 where the dose proportionality was evaluated the mean $C_{max}$ and AUC values at 24 hours increased linearly (21 to 150 µg /dose) with current levels of 70 µA to 430 µA. In the study C-97-001 the correlation between the estimated in vitro fentanyl dose and the in-vivo fentanyl dose absorbed was also high, and the mean prediction error was low, less than 10%. In the study C-97-001 it was shown also that the pharmacokinetic parameters following administration of 25 µg and 40 µg IONSYS system were dose proportional.

Time dependency has been sufficiently evaluated, fentanyl hydrochloride absorbed by the IONSYS increases as a function of time, and this increase is independent of the frequency of dosing. Steady state is not achieved during the first 24 hours of treatment. In the treatment of acute pain this is not optimal. Higher doses of opioids are commonly required in the initiation of pain treatment, and when optimal analgesia is achieved sufficient analgesic effect could be sustained with lower doses. In the summary of clinical pharmacology studies the applicant writes that in the studies C-94-067 and C-2001-009 steady state was reached by 20 to 23 hours. However, the longest application times of IONSYS were 24 hour, thus this approach does not allow to make any conclusions on multiple IONSYS applications.
The pharmacokinetics parameters of fentanyl hydrochloride after single and three applications of IONSYS evaluated in study C-94-068 are shown in the table below:

**Table**: Mean (SD) and range serum fentanyl hydrochloride pharmacokinetic values following IONSYS treatment for 20 and 68 hours

| | 1 day IONSYS<br>n = 25 | 3-days IONSYS<br>n = 25 | p-value |
|---|---|---|---|
| $C_{max}$ ng/ml | 0.3 (0.13)<br>0.13 - 0.71 | 0.48 (0.19)<br>0.26 - 0.99 | 0.0001 |
| $C_{pre}$ ng/ml | 0.21 (0.08) | 0.34 (0.13) | 0.0001 |
| $AUC_{20-25}/AUC_{68-73}$<br>ng•h/ml | 1.2 (0.55)<br>0.3 - 2.6 | 1.9 (0.71)<br>1.0 - 4.0 | 0.0001 |

- Special populations

The pharmacokinetics of fentanyl hydrochloride in postoperative patients seems to be similar to those in healthy subjects.

The pharmacokinetics of fentanyl hydrochloride from IONSYS in patients with renal impairment has not been determined.
As renal clearance of fentanyl is low, a decrease in renal function would not have a significant effect on the clearance.

The pharmacokinetics of fentanyl hydrochloride from IONSYS in patients with hepatic impairment has not been determined. In general fentanyl disposition appears to be affected more by hepatic blood flow than by hepatocellular function. Thus, it has been recommended that fentanyl doses need not be adjusted in the hepatically impaired patients.

Gender differences have been reported for hepatically metabolised drugs. Generally, those that are metabolised by CYP3A4 appear to be eliminated faster by women.
The effect of gender on the amount of fentanyl absorbed from IONSYS was evaluated in studies C-93-019 and C-94-060, which showed that gender does not have significant effect on fentanyl absorption. A combined analysis of data from studies C-97-001, C-94-067, C-2001-009 provides additional confirmation that gender does not affect fentanyl absorption.

The pharmacokinetics of fentanyl hydrochloride from IONSYS are scarcely studied in elderly patients, > 75 years old, and in children, < 12 years old.

- Pharmacokinetic interaction studies

The interactions of fentanyl hydrochloride, which is the active moiety in IONSYS, have not been evaluated. However, several drugs, which are commonly used during surgery, have a potential for drug-drug interaction with fentanyl. Potential interactions with potent CYP3A4 inhibitors such as Ritonavir and ketoconazole, which can reduce the clearance of fentanyl are mentioned in the SPC, section 4.5.

- Exposure relevant for safety evaluation

The analgesic plasma concentration of fentanyl is 1-2 ng/ml, and this was confirmed also in the present studies. In patients who received other concomitant opioids, e.g. morphine, lower plasma fentanyl concentration provided a sufficient analgesic efficacy. However, some patients required significantly higher plasma fentanyl concentrations for sufficient analgesic efficacy, e.g. after 80 sequential doses with the commercial intended IONSYS system one subject (n:o 110) developed serum fentanyl hydrochloride concentration of 6.6 ng/ml (study C-2001-009).

Some technical failures occurred, e.g. in the study C-2001-009 with the commercial intended IONSYS in Subject 102 the LED turned off early without beeping. In addition, the number of LED flashes was inconsistent with the doses given for this subject. This subject developed a high serum fentanyl concentration (Cmax 3.8 ng/ml).

**Pharmacodynamics**

- Mechanism of action

Fentanyl is an opioid analgesic, interacting mainly with μ-opiate receptors. Fentanyl binds to opiate receptors with higher binding affinity to μ- as compared to κ- or δ-opiate receptors. In a receptor binding assays using guinea big whole brain membrane dissociation constant value for fentanyl were 1.2±0.2 nM, 180±18 nM and 290±24 nM for μ-, δ- and κ-receptors, respectively.

Most of the effects of fentanyl are readily reversed by opioid-antagonists such as naloxone.

- Primary and Secondary pharmacology

*Primary Pharmacology*
Several studies have correlated fentanyl plasma concentration with analgesia (the desired effects) and respiratory effect (the most dangerous undesirable effect). However, the intensity of the effects correlates with the drug concentration at the site of action (effect site) and not necessarily the plasma concentration. For fentanyl the effect site is the opioid receptor in the brain and spinal cord.
In man a 100 µg dose of intramuscular fentanyl is approximately equivalent in analgesic activity to 10 mg of intramuscular morphine.
Based on the results of study C-2000-007, 287 µg of transdermal fentanyl hydrochloride with IONSYS is equivalent to 10 mg IV morphine.

*Secondary Pharmacology*
Beside analgesia, the administration of fentanyl may result in typical opioid-induced side effects such as respiratory depression, constipation, physical dependence and euphoria. Compared to morphine fentanyl is reported to have a more favourable safety margin towards cardiovascular, neurological, and metabolic effects. In the study C-2000-007 the incidence and severity of adverse effects was similar with IONSYS fentanyl hydrochloride and IV PCA morphine.

In general, the metabolites of fentanyl do not contribute to the analgesic activity, as demonstrated by their weak activity in a guinea pig ileum bioassay and two in vivo assays, the hot test plate in mice and the tail withdrawal test in rats.

Fentanyl concentrations greater than 1 ng/ml produce slight analgesia and ventilatory depression, those greater than 3 ng/ml yield additional analgesia and a 50% decrease in ventilatory response to carbon dioxide. Concentrations greater than 20 ng/ml cause loss of consciousness.

*Pharmacodynamic interactions*
The pharmacodynamic interactions with other analgesics, anaesthetics and other central nervous system depressants have not been evaluated. However, other medicinal products and substances may have significant interactions with transdermal fentanyl during the immediate postoperative period. E.g. in the Study C-2000-007 and C-95-016, where some patients were provided morphine for rescue analgesic, sufficient analgesic efficacy was achieved with a significantly lower plasma fentanyl concentrations than in patients receiving only fentanyl.

**Clinical efficacy**

- **Dose response studies**

Two dose-finding studies were conducted.
The first study (FEN-INT-6) evaluated 20µg, 40µg and 60µg fentanyl HCl administered by IV dosing, but mimicking the 10-minute infusion times of E-TRANS, in 150 in-patients who had undergone major abdominal surgery. Dose-response for patient global assessment was observed with 42%, 52% and 68% respectively reporting very good to excellent. Dose response was also observed for respiratory system adverse events. The applicant determined that 40µg fentanyl HCl provided the best balance of efficacy and tolerability.
The analgesic plasma concentration of 1-2 ng/ml of fentanyl was confirmed in this study.
The second study (C-93-023) compared 25µg fentanyl HCl in 79 patients following abdominal or orthopaedic surgery with 40µg fentanyl HCl in 174 patients in a 'similar patient population'. The study was not randomised, instead the two groups of patients were recruited sequentially. Lower efficacy and more respiratory system AE's were observed with the lower dose.

The proposed analgesic serum fentanyl hydrochloride concentration of 1 ng/ml is achieved with IONSYS after 36 sequential doses. However, there is a high variation in serum concentrations, although the mean is 1.1 (SD 0.5) the minimum is 0.3 and the maximum 2.5 ng/ml. After 18 sequential doses only 3 of 28 developed serum fentanyl hydrochloride concentration of 1 ng/ml (study C-2002-027).

In the pilot efficacy and safety study in the treatment of postoperative pain (study C-93-023) the individual plasma concentrations of fentanyl were between 1-2 ng/ml in the majority of patients, all were below 8 ng/ml.

- **Main studies**

An overview of the four main Phase III studies is given in the following Table

**Table: Overview of main Phase III efficacy and safety studies (Study C-2001-011, C-2000-008, C-95-016, C-2000-007)**

| Type of Study | Study No Location | Objectives | No. of Subjects; Population | Study Design/ Type of Control | Test Product(s); Dosage Regimen ; Route of Administration | Duration of Dosing |
|---|---|---|---|---|---|---|
| **Placebo-controlled Clinical Trials** | | | | | | |
| Safety and efficacy | C-2001-011[26] USA | Compare E-TRANS (fentanyl HCl) and E-TRANS (placebo) | 484 treated post-operative patients (n=244 in Treatment A, n=240 in Treatment B) | Multicentre, randomised, double-blind, parallel-group Placebo-controlled | A. E-TRANS (fentanyl HCl) 40 µg up to 6 doses/h B. E-TRANS (placebo) Each dose from each treatment administered over 10 min | Up to 24 h |
| Safety and efficacy | C-2000-008[25] USA | Compare E-TRANS (fentanyl HCl) and E-TRANS (placebo) | 205 treated post-operative patients (n=154 in Treatment A, n=51 in Treatment B) | Multicentre, randomised, double-blind, parallel-group Placebo-controlled | A. E-TRANS (fentanyl HCl) 40 µg up to 6 doses/h B. E-TRANS (placebo) Each dose from each treatment administered over 10 min | Up to 24 h |
| Safety and efficacy | C-95-016 New Zealand | Compare E-TRANS (fentanyl HCl) and E-TRANS (placebo) | 102 treated post-operative patients (n=77 in Treatment A, 25 in Treatment B) | Single-centre, parallel-group, double-blind Placebo-controlled | A. E-TRANS (fentanyl HCl) 40 µg up to 6 doses/h B. E-TRANS (placebo) Each dose from each treatment administered over 10 min, up to 80 doses available over 24 h | Up to 24 h |
| **Active-controlled Clinical Trial** | | | | | | |
| Safety and efficacy | C-2000-007[27] USA and Canada | Compare E-TRANS (fentanyl HCl) and IV PCA morphine | 636 treated post-operative patients (n=316 in Treatment A, n=320 in Treatment B) | Multicentre, randomised, stratified, open-label, parallel-group Active-controlled | A. E-TRANS (fentanyl HCl) 40 µg up to 6 doses/h, each dose administered over 10 min B. IV PCA morphine (1 mg/dose) up to 10 doses/h), each dose administered as a bolus, followed by a 5-min lockout period | Up to 72 h |

**PLACEBO-CONTROLLED STUDIES**

METHODS

Studies C-2001-011 and C2000-08 were multicentre, randomised, double-blind, placebo-controlled studies in acute moderate to severe post-operative pain in adult patients requiring parenteral opioid analgesics. The objective was to evaluate the safety and effectiveness of the IONSYS (fentanyl HCl) 40 µg system to placebo for the management of pain in the first 24 hours of postoperative pain.

C-95-016 is not described in this report as it is a single-centre study and therefore suffers potentially from a lack of generalisation. It had, however, a similar design to the other placebo-controlled studies and its results are generally consistent with those observed in the other trials.

*Study Participants*

The main inclusion and exclusion criteria were similar for the 2 controlled studies (C-2001-011 and C-2000-008) which are discussed below.

Main inclusion criteria

- Age 18 years or older of either sex
- In Post Anesthesia Care Unit (PACU) or recovery room for at least 30 minutes after major surgery (abdominal/thoracic or orthopedic bone) performed using general or regional anesthesia.
- Acute moderate or severe pain requiring parenteral opioids for at least 24 hours after surgery.
- Comfortable or titrated to comfort using IV opioids
- Pain score less than 5 on a scale of 0 to 10 five minutes after deep breathing and coughing.
- American Society of Anesthesiologists (ASA) physical status I, II, or III post-operatively.

Main exclusion criteria

- the patients were expected to have post-operative analgesia supplied by a continuous regional technique or had received a long-lasting intraoperative regional analgesic,
- were expected to require intensive care or another surgical procedure within 36 hours,
- received opioids other than morphine, fentanyl, sufentanil, or alfentanil intra-operatively and/or post-operatively except one dose of meperidine for shivering.
- Active systemic or local skin disease.
- Known or suspected opioid tolerance or history of opioid dependence.

*Treatments*

Following surgery (abdominal/ thoracic or somatic orthopaedic bone), patients were titrated to an acceptable level of comfort with i.v. opioid prior to randomisation.
Patients were allowed supplemental i.v. fentanyl during the first three hours of system application if unable to maintain comfort from study treatment alone. Other analgesics were not permitted, except acetaminophen for headache or fever reduction and a single dose of meperidine (for shivering) in the PACU or recovery room. In the event that the E-TRANS or placebo system fell off or did not respond to a dosing request, a replacement system was applied.

To complete the study, a patient had to complete at least 24 hours of treatment with IONSYS (fentanyl HCl) or placebo, be discharged from the hospital, or require no further parenteral opioid analgesia.

*Outcomes/endpoints*

The **primary efficacy endpoint** was the number of evaluable patients in each treatment group who terminated the study due to inadequate analgesia during the 24-hour treatment period. Evaluable patients were defined as those who completed three or more hours of IONSYS (fentanyl HCl) treatment.

Five **additional efficacy endpoints** were assessed as follows:
• patients who withdrew from the study ≥3 hours after treatment initiation for any reason;
• assessments of pain intensity on a numerical rating scale (JCAHO Pain Management Standards);
• patient global ratings of the method of analgesia;
• investigator global ratings of the method of analgesia;
• clinical use data (number of doses delivered, number of patients requiring retitration to comfort within 3 hours after application, patient feedback questionnaire, patient satisfaction questionnaire, system adhesion, assessment of suspected technical failures)

*Sample size*

In the main study C-2001-011, the sample size of 430 evaluable postoperative patients (215 patients in each treatment group) was planned for the study. The withdrawal rate for inadequate analgesia was assumed to be 40 % for the IONSYS placebo group and 25 % for the IONSYS (fentanyl HCl) group based on the study C-2000-008. The sample size provided approximately 90% power to detect a 15% difference in the withdrawal rate between treatments at the 0.05 significance level. To allow for a 10 % withdrawal rate prior to patients becoming evaluable, enrollment of up to 474 patients (237 in each treatment group) was planned.

In study C-2000-008, the sample size of 164 evaluable patients (123 on IONSYS (fentanyl HCl) and 41 on placebo) was selected to provide 90% power to demonstrate a 30% difference between treatments for the primary efficacy parameter at the 0.05 significance level. The withdrawal rate for inadequate analgesia was assumed to be 60 % for the IONSYS placebo group. To allow for a 30 % withdrawal rate prior to patients becoming evaluable, enrollment of up to 216 patients was planned. Baseline data were tested at the 0.10 significance level and efficacy analyses were tested at the 0.05 significance level. All tests were two sided. Data was pooled from both surgery strata and from all centres.

*Randomisation*
In the placebo controlled studies, patients were randomised to E-TRANS or placebo in a 3:1 (study 008) or 1:1 (study 011) ratio. In study C-2001-011, patients were supposed to have had a baseline pain score less than 5 on a scale of 0-10.

*Blinding (masking)*
To maintain blinding in these studies, placebo IONSYS (fentanyl HCl) systems were identical to active systems in appearance and operation except that the circuitry was modified to shunt electrical current and prevent drug delivery in placebo. Only the contract packager had access to the randomization code identifying the study drug assignment by the carton packaging/randomisation number.

*Statistical methods*
The primary endpoint ( proportion of patients withdrawing from the study due to inadequate pain control) was analysed primarily by chi-squared test and supportively by logistic regression investigating the influence of baseline covariates. The primary analysis was conducted on the population of evaluable patients, excluding patients who discontinued in the first 3 hours of study. An all-treated-patients (ATP) analysis was also conducted.
Secondary endpoints included assessments of withdrawal for any reason between 3 and 24 hours, pain intensity and patient and investigator ratings.
Pain was recorded on a 0-100 mm visual analogue scale (VAS) for study 008 and on a 0-10 verbal scale in study 011.

RESULTS

*Participant flow and recruitment*

Study 011

630 patients were screened in 20 sites in the US.
Of these, 484 patients were randomised to treatment (244 to E-TRANS and 240 to placebo). Of these, 439 completed 3 hours treatment (235 on E-TRANS and 204 on placebo).
According to the sample size calculations, a withdrawal rate for inadequate analgesia was assumed to be 40 % for the IONSYS placebo group and 25 % for the IONSYS fentanyl group. A 10 % withdrawal rate prior to patients becoming evaluable was expected. A total of 430 evaluable postoperative patients (215 per treatment group) were needed. This goal was reached.

Study 008:

232 patients were screened in 10 sites in the US.
Of these, 205 patients were randomised to treatment (154 to E-TRANS and 51 to placebo). Of these, 189 completed 3 hours treatment (142 on E-TRANS and 47 on placebo).
According to the sample size calculations, the withdrawal rate for inadequate analgesia was assumed to be 60 % for the IONSYS placebo and a total of 164 evaluable postoperative patients were needed. To allow for a 30 % withdrawal rate prior to patients becoming evaluable, enrolment of up to 216 patients was planned. The enrolment goal was reached.

*Baseline data*

The sex and age distributions of the patients were well balanced between the two treatment groups. However, the overall patient population was mainly female and Caucasian.
The distribution of ASA physical status was more balanced in the treated patients, which can be regarded as a more important patient population in this superiority trial. Further, the number of ASA III patients is considered sufficient in the overall study population. Patients with ASA physical status IV were excluded.

In the following Table the proportion of elderly patients in each of the 3 ASA categories are presented.

**TABLE 19-1**
**Proportion of Elderly Patients by Preoperative ASA Status**
**(All Treated Patients)**

| Study | ASA | <65 years | ≥65 years |
|---|---|---|---|
| C-2001-011 | I | 51 (14.2%) | 4 (3.2%) |
| | II | 256 (71.3%) | 69 (55.2%) |
| | III | 52 (14.5%) | 52 (41.6%) |
| C-2000-008 | I | 29(18.1%) | 2 (4.4%) |
| | II | 112 (70.0%) | 23 (51.1%) |
| | III | 19 (11.9%) | 20 (44.4%) |
| C-9[illegible]-16 | I | 71 (75.5%) | 6 (75%) |
| | II | 21 (22.3%) | 2 (25%) |
| | III | 2 (2.1%) | 0 |
| C-2000-007 | I | 107 (21.4%) | 1 (0.74%) |
| | II | 342 (68.4%) | 90 (66.2%) |
| | III | 51 (10.2%) | 45 (33.1%) |

Source: \\ap22clin\Work\EMEA 041118\clinical_aspects_tables\q19\ageasa16.lst, ageasa11.lst, ageasa7.lst, ageasa8.lst,

The majority of the elderly patients had ASA status II and III.
The following statement is mentioned in the SmPC (Section 4.4): The safety of IONSYS has not been studied in patients with ASA IV functional status".

The baseline mean pain intensity scores, taken immediately before the application of study medication (Hour 0), were similar for evaluable patients randomised to IONSYS (fentanyl HCl) (3.0) and placebo (3.1). However, the CHMP required the applicant to provide the full data of the pain intensity scores not only at Hour 0 but also at Hour 3 to confirm that the groups are comparable at the start of the evaluable period in the placebo-controlled studies. The scores are summarised in the table below.

**TABLE 1-2**
**Mean Pain Intensity Scores at Hours 0, 3, and Last Mean Score (Placebo-Controlled Studies: All Treated Patients)**

| Study | Hours Post-enrollment | IONSYS™ fentanyl, 40 mcg | | Placebo | |
|---|---|---|---|---|---|
| | | n | Mean (SEM) | n | Mean (SEM) |
| C-2001-011 | 0 | 244 | 3.0 (0.08) | 240 | 3.1 (0.08) |
| | 3 | 204 | 3.4 (0.13) | 188 | 4.0 (0.17) |
| | Mean Last | 244 | 3.5 (0.16) | 240 | 3.4 (0.17) |
| C-2000-008 | 0 | 154 | 42.7 (1.88) | 51 | 44.4 (3.04) |
| | 3 | 119 | 37.3 (2.14) | 37 | 38.0 (3.89) |
| | Mean Last | 154 | 33.7 (2.38) | 51 | 43.0 (4.41) |
| C-95-016 | 0 | 77 | 31.6 (1.51) | 25 | 34.4 (2.97) |
| | 3 | 77 | 31.6 (1.88) | 21 | 40.2 (4.12 ) |
| | Mean Last | 77 | 20.6 (1.93) | 25 | 35.7 (5.32) |

Note: (1) Treatment duration for the placebo-controlled studies was up to 24 hours.
(2) Pain intensity in C-2001-011 was measured by a 0-10 numeric scale, pain intensity in C-2000-008 and C-95-016 was measured by a 0-100 mm visual analog scale.

The reasons for withdrawal are given in the following table:

**TABLE 1-4**
**Reasons for Early Discontinuation During Hours 0 – 3 (Placebo-Controlled Studies: All Treated Patients)**

| Study | Withdrawal Category | IONSYS™ fentanyl 40 mcg | Placebo |
|---|---|---|---|
| C-2001-011 | Any reason | 9/244 (3.7%) | 36/240 (15.0%) |
| | Inadequate analgesia | 6/244 (2.5%) | 28/240 (11.7%) |
| | Withdrew consent | 1/244 | 2/240 |
| | Adverse event | 1/244 | 0 |
| | Protocol violation | 1/244 | 0 |
| | Suspected technical failure | 0 | 5/240 |
| | Other | 0 | 1/240 |
| C-2000-008 | Any reason | 12/154 (7.8%) | 4/51 (7.8%) |
| | Inadequate analgesia | 12/154 (7.8%) | 4/51 (7.8%) |
| C-95-016 | Any reason | 0 | 3/25 (12.0%) |
| | Inadequate analgesia | 0 | 0 |
| | Suspected technical failure | 0 | 3/25 |

The CHMP was of the opinion that whilst the randomisation should ensure balance between the treatment groups at baseline (Hour 0), exclusions post-baseline from the randomised groups may be differential and may therefore introduce a bias into the primary statistical analysis, which included only those evaluable patients participating in hours 3-24 of the study.

Similarly, in study 008, the second pivotal placebo-controlled study, the direction of the bias is also unclear as the proportion of withdrawals due to inadequate analgesia is similar in each treatment group. Given this similarity however, it is assumed that the magnitude of the bias will not be large. However, the all-treated-patients analysis is not so affected. In this population, patients randomised to IONSYS have access to both IONSYS and supplemental i.v. fentanyl as needed for 0-3 hours. Patients randomised to placebo have only the i.v. fentanyl. Therefore this 'all-patients' population provides a true comparison of IONSYS versus placebo (plus i.v. fentanyl in both groups from Hours 0-3) over 24 hours without the complications of defining evaluable patients and excluding withdrawals up to Hour 3. On the primary endpoint of patient withdrawals, the all-treated-patients population is highly statistically significant in two studies and borderline in the third.

*Outcomes and estimation*

Primary efficacy endpoint:

- Study C-2001-011

The table below summarises the results for the primary efficacy variable. For the evaluable patients 116/204 (56.9 %) in the placebo group and 64/235 (27.2 %) in the IONSYS (fentanyl HCl) group discontinued from the study due to inadequate pain relief after the first 3 hours of treatment.

**Table**: Withdrawals due to inadequate pain relief after the first 3 hours of treatment (study C-2001-011)

| | **E-TRANS®** (fentanyl) 40 µg | **Placebo** | **p-value** |
|---|---|---|---|
| **Evaluable Patients** (N) | 235 | 204 | |
| Withdrawals due to inadequate pain relief | 64 (27.2%) | 116 (56.9%) | <0.0001 |
| Duration of treatment[a] (h) | | | |
| Mean (SEM) | 7.8 (0.74) | 7.6 (0.48) | |
| Median (range) | 4.6 (3.0-22.5) | 5.4 (3.0-22.1) | |
| **Treated Patients** (N) | 244 | 240 | |
| Withdrawals due to inadequate pain relief | 70 (28.7%) | 144 (60.0%) | <0.0001 |
| Duration of treatment[a] (h) | | | |
| Mean (SEM) | 7.3 (0.70) | 6.5 (0.43) | |
| Median (range) | 4.3 (1.1-22.5) | 4.2 (1.0-22.1) | |

[a] For patients who withdrew due to inadequate analgesia

The results show that there was a statistically significant difference in the withdrawal rate due to inadequate analgesia between the IONSYS (fentanyl HCl) group and the placebo group in the evaluable patients. The more conservative approach with all treated patients in the analysis set included showed similar results. Even though the ITT-population analysis was performed as a secondary one for efficacy endpoint, the results led to essentially the same conclusions as the analysis in evaluable patients and increased confidence in the results. The difference between the two treatments is considered clinically relevant.

- Study C-2000-008

The primary efficacy endpoint was defined as the number of evaluable patients in each treatment group who withdrew from the trial because of inadequate pain control during the 24 hour treatment period, i.e., from 3 to 24 hours after beginning IONSYS (fentanyl HCl) treatment. Evaluable patients were defined as those who completed three or more hours of IONSYS (fentanyl HCl) treatment.

The tables and figures below summarise the results for the primary efficacy variable.

**Table**: Withdrawals due to inadequate pain relief (study C-2000-008)

| | E-TRANS® (fentanyl) 40 µg | Placebo | p-value |
|---|---|---|---|
| **Evaluable Patients** (N) | 142 | 47 | |
| Withdrawals due to inadequate pain relief | 36 (25.4%) | 19 (40.4%) | 0.0486 |
| Duration of treatment[a] (h) | | | |
| Mean (SEM) | 6.5 (0.84) | 6.6 (1.17) | |
| Median (range) | 4.2 (3.0-21.0) | 4.8 (3.0-21.5) | |
| **All Treated Patients** (N) | 154 | 51 | |
| Withdrawals due to inadequate pain relief | 48 (31.2%) | 23 (45.1%) | 0.0700 |
| Duration of treatment[a] (h) | | | |
| Mean (SEM) | 5.3 (0.69) | 5.7 (1.05) | |
| Median (range) | 4.0 (1.3-21.0) | 4.0 (1.2-21.5) | |
| **Treated Patients with PACU Pain <75** (N) | 121 | 45 | |
| Withdrawals due to inadequate pain relief | 30 (24.8%) | 20 (44.4%) | 0.0142 |
| Duration of treatment[a] (h) | | | |
| Mean (SEM) | 4.6 (0.58) | 6.1 (1.16) | |
| Median (range) | 4.0 (1.3-16.8) | 4.2 (1.3-21.5) | |

[a] For patients who withdrew due to inadequate analgesia

In the evaluable patients and in the ad hoc analysis of patients with PACU pain score less than 75 there is a statistically significant difference between the two treatment groups. However, the primary efficacy endpoint in all randomized patients is not statistically significantly different between IONSYS (fentanyl HCl) and placebo. The result with inference to the all randomized population does not support the results obtained in the less conservative analysis. The results of this study are considered to provide only borderline evidence of the efficacy of the product.

Additional efficacy endpoints

- Study C-2001-011

The additional efficacy endpoints included patients who withdrew from the study ≥3 hours after treatment initiation for any reason, assessment of pain intensity on a numerical rating scale, patient global ratings of the method of analgesia, investigator global ratings of the method of analgesia, and clinical use data.

The efficacy results including the primary efficacy endpoint in evaluable patients are presented in the following table:

**Table**: Efficacy results in evaluable patients (study C-2001-011)

| Efficacy Variable | E-TRANS (fentanyl HCl) (n=235) | | E-TRANS (placebo) (n=204) | | p-value |
|---|---|---|---|---|---|
| **Proportion of Dropouts** | | | | | |
| Inadequate analgesia | 64 | (27.2%) | 116 | (56.9%) | <0.0001 |
| Any reason | 81 | (34.5%) | 128 | (62.7%) | <0.0001 |
| **Global Assessment of Excellent or Good** | | | | | |
| Patient | 179 | (76.2%) | 106 | (52.0%) | <0.0001 |
| Investigator | 176 | (74.9%) | 107 | (52.5%) | <0.0001 |
| **Pain Intensity** | | | | | |
| Last mean pain intensity | 3.4 | | 5.3 | | <0.0001 |

Shaded areas denote primary efficacy results. Pain intensity in C-2001-011 was rated on a verbal numerical rating scale (0–10).

*The additional efficacy endpoints support the superiority of the IONSYS (fentanyl HCl) over placebo in evaluable and all treated patients.*

The overall feedback from the system operation was positive in evaluable patients.

- Study C-2000-008

The results are presented in the following table:

**Table**: Efficacy results in evaluable patients (study C-2000-008)

| Efficacy Variable | E-TRANS (fentanyl HCl) (n=142) | | E-TRANS (placebo) (n=47) | | p-value |
|---|---|---|---|---|---|
| **Proportion of Dropouts** | | | | | |
| Inadequate analgesia | 36 | (25.4%) | 19 | (40.4%) | 0.0486 |
| Any reason | 46 | (32.4%) | 25 | (53.2%) | 0.0107 |
| **Global Assessment of Excellent or Good** | | | | | |
| Patient | 96 | (67.6%) | 25 | (53.2%) | 0.0743 |
| Investigator | 102 | (71.8%) | 25 | (53.2%) | 0.0183 |
| **Pain Intensity** | | | | | |
| Last mean pain intensity | 30.9 | | 40.8 | | 0.0474 |

Shaded areas denote primary efficacy results. Pain intensity in C-2000-008 was rated on a visual analogue scale (0–100 mm).

The efficacy results including the primary efficacy endpoint in all treated patients with baseline pain scored < 75 is presented in the following table.

**Table**: Efficacy results in all treated patients with baseline pain scored < 75 (study C-2000-008)

| Efficacy Variable | E-TRANS (fentanyl HCl) (n=121) | | E-TRANS (placebo) (n=45) | | p-value |
|---|---|---|---|---|---|
| **Proportion of Dropouts** | | | | | |
| Inadequate analgesia | 30 | (24.8%) | 20 | (44.4%) | 0.0142 |
| Any reason | 38 | (31.4%) | 25 | (55.6%) | 0.0044 |
| **Global Assessment of Excellent or Good** | | | | | |
| Patient | 82 | (67.8%) | 22 | (48.9%) | 0.0254 |
| Investigator | 86 | (71.1%) | 22 | (48.9%) | 0.0077 |
| **Pain Intensity** | | | | | |
| Last mean pain intensity | 29.0 | | 42.5 | | 0.0083 |

Pain intensity in C-2000-008 was rated on a visual analogue scale (0-100 mm)

The results of the additional efficacy endpoints in the ad hoc analysis are supportive for the primary endpoint ad hoc analysis.

**OPEN-LABEL STUDY C-2000-007**

METHODS

Study C-2000-007 was a multicenter, randomised, open-label, parallel-group study to compare the safety and efficacy of IONSYS (fentanyl HCl) system treatment with IV PCA (Patient Controlled Analgesia) morphine treatment for the management of moderate to severe postoperative pain.

The design and patient population of this study was essentially similar to the two placebo-controlled studies described above, but IV PCA morphine (administered as a 1 mg bolus on demand with a 5-minute lock-out interval to a maximum of 10 mg per hour) replaced the placebo control group and study treatment could be continued for 72 hours.

The primary efficacy measure in this study was the patient global assessment of the method of analgesia at the end of the first 24-hour treatment period. For the primary analysis, the patient global assessment was dichotomised such that a successful treatment outcome was defined as a good or excellence response. Thus, in fact, the primary endpoint is the proportion of patients with successful

treatment outcome according to patient global assessments. In this study, the lower limit of 95 % CI exceeded the pre-defined non-inferiority margin – 10 %.
As an additional efficacy endpoint patient global assessments were also solicited at the 48- and 72-hour time point or at the time of premature discontinuation. The investigator global assessment of pain intensity was evaluated at the 48- and 72-hour time point as in study C-2000-008. The pain intensity measurement was similar as in the study C-2000-008. The clinical use data was assessed as in the study C-2000-008.

Assuming a success rate of 80 % for both IONSYS (fentanyl HCl) and the IV PCA morphine treatment groups, a sample size of 252 patients was needed for each treatment. To allow for a 20 % dropout rate before the patients´ becoming evaluable, an enrolment up to 630 patients was obtained for this study.

Patients who met all of the study entry requirements were randomized in an l-to-l ratio IONSYS (fentanyl HCI) or IV PCA morphine using an Interactive Voice Response System (IVRS) randomisation procedure.

The primary efficacy analyses were performed using data from all evaluable patients. The secondary efficacy analysis was performed in all treated patients. All evaluable patients were defined as those who reached the 3-hour time point in the study.

All tests for the final efficacy values were performed at the 0.05 significance levels. A two-sided 95 % confidence interval (CI) of the difference in the success rate (proportion of excellent/good patients global assessments) was calculated. This was adequate to define therapeutic equivalence or non-inferiority. The two treatments were considered therapeutically equivalent as the 95% CI of the difference in success rate fell within ±10 % based on two one-sided tests with $\alpha = 0.025$ and a maximum acceptable difference of 10%.

RESULTS

*Participants flow:*
Thirty-three sites in the United States (n = 29) and Canada (n=4) a total of 726 patients for this study.
The study period was from 18 September 2000 to 11 March 2001.
A total of 726 patients was screened in 33 sites in the US.
Of these, 636 patients were randomised to treatment (316 to E-TRANS and 320 to IV PCA morphine).
Of these, 626 completed 3 hours treatment (310 on E-TRANS and 316 on placebo).

*Baseline data*

The pain intensity score data is presented in the table below. The mean pain intensity scores for evaluable patients were similar for the two treatment groups, 45.6 for the ionsys (fentanyl HCl) groups and 44.7 in the IV PCA morphine group, p =0.6384. Similar pain scores were observed for all treated patients.

**Table:** Pre-enrolment pain intensity scores in evaluable patients (study C-2000-007)

| | E-TRANS(fentanyl) 40 µg (n=310) | IV PCA morphine (n=316) | Total (n=626) | p-value |
|---|---|---|---|---|
| Pain Intensity (mm on VAS) | | | | |
| <25 | 55 (17.7%) | 64 (20.3%) | 119 (19.0%) | |
| 25 - <50 | 125 (40.3%) | 121 (38.3%) | 246 (39.3%) | |
| 50 - <75 | 94 (30.3%) | 95 (30.1%) | 189 (30.2%) | |
| ≥ 75 | 36 (11.6%) | 34 (10.8%) | 70 (11.2%) | |
| Missing | 0 | 2 ( 0.6%) | 2 ( 0.3%) | |
| Statistics | | | | |
| n | 310 ( 100%) | 314 (99.4%) | 624 (99.7%) | 0.6384 |
| Mean (SEM) | 45.6 ( 1.34) | 44.7 ( 1.30) | 45.1 ( 0.93) | |
| Median | 44.5 | 45.0 | 45.0 | |
| Range | 0 to 100 | 0 to 100 | 0 to 100 | |
| Missing | 0 | 2 ( 0.6%) | 2 ( 0.3%) | |

Note: p-value was calculated using ANOVA.

*Outcomes and estimation*

Results on the primary efficacy variable were as follows:

| Population | Outcome | E-TRANS | i.v. PCA morphine | p- value | 95% CI |
|---|---|---|---|---|---|
| Evaluable | Success | 74.8% | 77.8% | 0.376 | (-9.7%, 3.7%) |
| | Missing | 1.0% | 1.9% | | |
| All-treated | Success | 73.7% | 76.9% | 0.358 | (-9.9%, 3.5%) |
| | Missing | 0.9% | 1.9% | | |

Exclusions prior to 3 hours follow-up do not appear to have affected the primary efficacy results, which appear to provide borderline evidence of non-inferiority.

Results on secondary endpoints were generally supportive of the primary results. There was no apparent drop-off in efficacy for E-TRANS from 24-72 hours. Patients remaining on treatment continued to do as well as patients on i.v. PCA morphine.

However, although the system has been demonstrated to approach therapeutically equivalence to standard IV PCA morphine regime, the evidence of non-inferiority to IV PCA morphine is not considered to be sufficiently robust. The phraseology of the primary end-point question in the comparative study may have biased the results of the trial. In particular the questions on patient/investigator preference such as ease of preparation and administration or comfort during use may have influenced the trial subjects' response. Furthermore, because of the open-label design of this study. the results are considered only as supportive for the efficacy of the product

Therefore, the SPC includes a no claim of similar efficacy between IONSYS and IV PCA morphine .

- Clinical studies in special populations

*Elderly patients over 75 years*

As too few elderly patients >75 years old have been included in the clinical trials, the following text has been included in the SPC: Elderly: Limited data on the pharmacokinetics, safety and efficacy are available for the use of IONSYS™ in patients > 75 years. Elderly patients should be observed carefully for signs of fentanyl toxicity

*Patients with Body Mass Index (BMI) > 40*

The difference between active and placebo treatments is maintained in the placebo-controlled trials except in patients with BMI > 40, where the difference loses statistical significance due to small numbers. In the active-controlled study, there were non-significant differences between treatments in all BMI groups.
The following statement has been added in the SPC: "Efficacy and safety in patients with BMI > 40 has not been established."

*Patients with thoracic/chest and upper abdominal surgeries*

Due to small number of patients with thoracic/chest and upper abdominal surgeries the following statement has been added in the SPC: "Only limited data are available in patients with thoracic/chest and upper abdominal surgeries. IONSYS should therefore be used with caution in these patients."

*Patients with cystic fibrosis*

As no such patients have been included in the clinical trials, the following statement has been added in the SPC "Efficacy and safety in patients with cystic fibrosis has not been established."

*Study in paediatric patients*

The current application for marketing authorisation does not include use in paediatric patients, and as mentioned by the applicant, no conclusions of the efficacy in paediatric population can be drawn and the applicant claims none. This study is considered to support the postoperative fentanyl PCA regimen in general.

**Study C-2000-005:** An Open Evaluation of Safety and Clinical Utility of IONSYS (fentanyl) for Management of Post-Operative Pain in Children and Adolescents

Methods
This was a multicentre, open-label study in which paediatric postoperative patients received IONSYS (fentanyl HCl) for up to 3 consecutive days.
All patients initiated treatment with IONSYS (fentanyl HCl) 25 µg and were allowed supplemental medication (IV fentanyl) during the first 3 hours of treatment. If the patient was having inadequate analgesia 3 hours after the system was first applied, the 25 µg system could be removed and replaced with the 40 µg system for the remainder of that 24-hour treatment period. At the end of each 24-hour treatment period, the patient could either continue at the higher dose, return to the lower dose, or stop treatment if pain relief was inadequate. Patients who returned to the lower dose had to remain at this dose level for the remainder of the study.

Up to 150 patients were planned for enrolment to ensure 120 evaluable patients. Patients were considered evaluable if they received at least 3 hours of treatment with IONSYS (fentanyl HCl). A total of 121 patients were treated in the study.

Results
One hundred and three (85.1%) of the 121 paediatric patients (mean age 10.5 years) enrolled in this study completed the study (defined as completed either 72 hours of treatment or prior to 72 hours were discharged from the hospital or had no further need for parenteral opioid analgesia). Of the total 121 patients treated, 38 (31.4%) were in the 20.0-29.9 kg group, 35 (28.9%) were in the 30.0-39.9 kg and 48 (39.7%) were in the ≥40 kg group. Eighteen patients discontinued from the study prematurely.

Adverse events were the most common reason for termination (n=9), followed by withdrawal of consent (n=3), other (n=3), inadequate analgesia (n=2) and protocol violation (n=1).

Overall, investigators assessed the IONSYS (fentanyl HCl) systems as easy for all patients to use and suitable for the patient population, based on the fact that 97.5% of patients did not have difficulty using the system and 97.5% of patients did not require further assistance/instruction with the system over and above the usual assistance/instruction given to patients using PCA.

The following results are presented only for the patients who had the IONSYS (fentanyl HCl) 40 µg system employed. Of the 28 patients who had the IONSYS (fentanyl HCl) dose increased from 25 µg to 40 µg, 19 (67.9%) rated IONSYS (fentanyl HCl) a fair or poor method of pain control immediately before their dose increase. Fourteen of these 19 patients improved their ratings to either good or excellent at their final PGA assessment after increasing to the 40 µg dose. Of the 28 patients who increased from 25 µg to 40 µg, 17 (60.7%) received an IGA rating of fair or poor for IONSYS (fentanyl HCl) 25 µg as a method of pain control immediately before their dose increase. For 15 of these 17 patients, their ratings were improved to good or excellent at the last assessment after increasing to the 40 µg dose. At the last assessment using the 40 µg dose system, the mean pain intensity VAS score for these 28 patients was 35.9.

Since this study only evaluated the utility and safety of the 40 µg system in a subset of patients who had experienced inadequate analgesia while using the 25 µg dose system.

- Supportive studies

There were four uncontrolled studies. All these studies were conducted according to GCP standards. Study C-93-023 evaluated adult patients in the first 24 hours after surgery whereas study C-94-043, the follow-on study to C-93-023, assessed patients on days 2 and 3. Study C-95-019 assessed patients who had "short stay" surgery, e.g. laparoscopic or arthroscopic procedures. Paediatric patients, aged between 6 and 15 years, who required more than 25 µg for fentanyl after major surgery were included in study C-2000-005. Treatment assignment in the uncontrolled studies was not randomised and all treatments were administered open-label. The timing of treatment administration was similar to that in the placebo-controlled studies. Except for C-2000-005, which used the commercial IONSYS (fentanyl HCl) system, uncontrolled studies employed a reusable electronic controller that was housed separately from the disposable drug hydrogels. The electronic controller could be adjusted to provide 40 µg or 25 µg per 10 minutes as required by the protocol.

An overview of the four supportive Phase III studies is given in Table below:

**Table**: Overview of supportive Phase III studies (C-93-023, C94-043, C-95-019, C-2000-005)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Safety and efficacy | C-93-023 | Evaluate the safety and efficacy of E-TRANS® fentanyl | 253 postoperative patients | Open-label, sequential group dose escalation | Part 1. E-TRANS® fentanyl up to six 25 µg doses/h (n=79)<br>Part 2. E-TRANS® fentanyl up to six 40 µg doses/h (n=174)<br>Each dose delivered over 10 min | Up to 24 h | Complete; full |
| Safety and efficacy | C-94-043 | Safety and efficacy on postoperative days 2 and 3 (first 24 h in C-93-023) | 115 postoperative patients continued from C-93-023 | Open-label | A. E-TRANS® fentanyl up to six 40 µg doses/h, each dose delivered over 10 min | Up to 48 h | Complete; full |
| Safety and efficacy | C-95-019 | Safety and efficacy following short-stay surgical procedures | 78 postoperative patients who had short-stay surgery | Open-label | A. E-TRANS® fentanyl up to six 40 µg doses/h, each dose delivered over 10 min | Up to 48 h | Complete; full |
| Safety and efficacy | C-2000-005 | Safety and clinical utility following major surgery | 121 pediatric post-operative patients, 6–15 years of age | Multicenter, open-label | A. E-TRANS® fentanyl up to six 25 µg doses/h (n=93)<br>B. E-TRANS® fentanyl up to six 40 µg doses/h (n=28)<br>Each dose from each treatment delivered over 10 min<br>All patients started with Treatment A, titration up to Treatment B was allowed if patients had uncontrolled pain >3 h after treatment initiation | Up to 72 h | Complete; full |

Results
Overall the results of these studies indicate that IONSYS (fentanyl HCl) 40 µg provides good to excellent analgesia in most patients.

- Discussion on clinical efficacy

The evidence of the efficacy of the product is based mainly on the pivotal study C-2001-011 while the studies C-2000-008, C-95-016 and C-2000-007 are considered supportive.

In the scientific advice given in 1999 it was stated that in the placebo-controlled studies the primary criterion is, essentially, the proportion of patients experiencing treatment failure at three hours. It was concluded that the criterion seemed reasonable and the relatively short time would reduce the exposure of patients to placebo. Patients Global Assessment was agreed to provide an integration of pain control over 24 hours and it was concluded to be a reasonable primary efficacy criteria. However, the applicant chose to assess the primary efficacy criteria, treatment failure, after 3 hours when no rescue medication was allowed.

The CHMP was of the opinion that whilst the randomisation should ensure balance between the treatment groups at baseline (Hour 0), exclusions post-baseline from the randomised groups may be differential and may therefore introduce a bias into the primary statistical analysis, which included only those evaluable patients participating in hours 3-24 of the study. Following further justification by the applicant, it was concluded that the study designs were not optimal and that assessment is complicated because of the exclusion of early withdrawals and the definition of evaluable patients and therefore, the primary analyses were likely to be biased. Nevertheless, given the results in the all-patients population, it is considered that evidence of efficacy has been established

The results of the pivotal study C-2001-011 show that there is a statistically significant difference in the primary efficacy criteria, withdrawal rate due to inadequate analgesia, between the IONSYS (fentanyl HCl) group and the placebo group in the evaluable patients. The more conservative approach with all treated patients showed similar results. Even though the ITT-population analysis was performed as a secondary one for efficacy endpoint, the results led to essentially the same conclusions as the analysis in evaluable patients. The difference between the two treatments is considered to be clinically relevant.
After discussion with CHMP, the following statement has been added in the SPC:'Patients should be titrated to an acceptable level of analgesia prior to initiating the use of IONSYS'

In the study C-2001-011, the additional efficacy parameters, defined as Patient or Investigator Global Assessments, pain intensity and clinical use data, supported the superiority of IONSYS over placebo.

In the study C-2000-008 the patient's global assessment of excellent or good was not statistically significantly different between the IONSYS (fentanyl HCl) treatment and placebo in evaluable and all treated patients but was statistically significant in the investigators' assessment. However, the last mean pain intensity scores were not significantly different in the two treatment groups in the all treated population.

In study C-95-016 the additional efficacy parameters supported the conclusions from the primary efficacy parameters.

The CHMP requested subgroup analyses in order to demonstrate the consistency of effect of IONSYS™ in different sub-group of patients.
The data submitted by the applicant showed that E-TRANS was efficacious among all subgroups, including ASA status, somatic versus visceral pain, baseline pain score, age, gender, race, and BMI. The magnitude of the treatment effect was clinically significant although in some subgroups (eg. patients with Body Mass Index (BMI) > 40, age > 75years) statistical significance was not reached due to the small number of patients.

In the active-controlled study, non-inferiority was to be concluded if the difference in proportion of successes was < 10% in favour of i.v. morphine. Despite a similar proportion of 'success' in both treatment groups, it is considered that non-inferiority has not been robustly substantiated because the phraseology of the question relating to the primary endpoint. It is considered likely that patients would not judge the treatments solely on their efficacy with regards pain control but also on their comfort, ease of administration etc. The lack of a formal demonstration of non-inferiority is considered unimportant with regards overall evidence of efficacy.

Finally, the CHMP considered that data on time from activation of the patch to time of relief was insufficient, and requested that further reassurance should be provided that patients would not receive an overdose of fentanyl due to delayed onset of effect and repeated activation of the device. The applicant justified that the onset of analgesia was not chosen as an endpoint in the IONSYS clinical trials because of the principle of patient self-titration in contrast to studies in which a single large analgesic dose is expected to relieve higher baseline. The applicant also argued that data from patient controlled analgesia dosing with morphine and IV fentanyl, pharmacokinetic data, comparative dosing data, and safety data on E-TRANS support the lack of a problem with potential overdose due to excessive demand for analgesia. They also argue that because high doses of fentanyl would be sufficiently sedating to inhibit the patient from self – delivering more drug. The CHMP considered that these arguments are questionable as extrapolations of clinical and pharmacokinetic data from a different drug and extrapolations of safety and efficacy of fentanyl from different dosages regimes and different modes of systemic delivery are not appropriate to draw conclusions on safety. Therefore, the CHMP requested the applicant to provide clinical trial data on the time taken to obtain acceptable analgesia after activating the device as a follow-up measure.

**Clinical safety**

Safety evaluation based on 4 controlled studies and 7 uncontrolled studies, 4 of which were conducted with the 40 µg system and 3 with the lower 25 µg system. Data from 10 pharmacokinetic studies in naltrexone blocked healthy adult subjects and 1 pharmacokinetic study in paediatric intraoperative patients were also included in the overall safety evaluation.

- Patient exposure

The list of clinical studies contributing to safety is presented in the following table:

**Table:** Grouping of studies contributing to safety

| Grouping of Studies | Studies Included |
|---|---|
| All clinical studies in patients: | Includes controlled, uncontrolled and stopped studies |
| Controlled studies | Placebo controlled: Studies C-95-016, C-2000-008[23], C-2001-011[24]<br>Active controlled: C-2000-007[22] |
| Uncontrolled studies* | Studies C-93-023, C-94-043, C-95-019, C-96-020, C-2000-005, C-2000-006, C-2000-009 |
| Stopped studies* | Studies C-94-057, C-94-058, C-94-059, C-96-055, C-96-056, C-96-057 |
| Pharmacokinetic studies in healthy adult subjects | Commercial formulation: Studies C-94-060, C-94-067, C-94-068, C-96-009, C-97-001, C-2001-009, C-2002-027<br>Non-commercial formulation: Studies C-92-038, C-93-019<br>Commercial formulation: 15-minute dosing: Study C-98-013 |
| Pharmacokinetic study in paediatric patients | Study C-2001-006 |

* Although presented as separate groups, uncontrolled and stopped studies are not discussed separately in this Summary of Safety because of the lack of comparator groups in the uncontrolled studies and the small number of patients in the stopped studies. Data from these two groups are included under "All clinical studies in patients."

Five clinical pharmacology supporting studies, five wearing studies with non-drug containing systems, and a dose-ranging study using IV PCA fentanyl were also performed during the clinical development programme. Data from these 11 studies was not pooled.

All patients who had at least one IONSYS (fentanyl HCl) system applied, IV PCA device enabled or IM injection received were considered treated and were included in the safety analysis. A total of 2660 patients, including 567 patients >65 years of age and 124 paediatric patients 5 to 17 years of age, were treated overall (referred to as "all clinical studies", i.e. controlled, uncontrolled and stopped studies, see above table). Three hundred and forty (340) healthy subjects and 25 paediatric patients were treated during the pharmacokinetic studies. Of the 2660 patients in all clinical studies, 1142 were treated with the IONSYS (fentanyl HCl) 40 µg system and the remainder were treated with either the 25 µg system, placebo or active control.

In the controlled studies, all 791 patients treated with IONSYS (fentanyl HCl) 40 µg were adult, predominantly female (72.1%), and Caucasian (79.0%), with a mean age of 51.5 years (range, 18 to 90 years). Over 90% of patients entered the study following orthopaedic bone or lower abdominal surgeries. Most patients were in good health post-operatively (ASA I 20.5%, ASA II 64.0%), but 15.5% were higher morbidity patients (ASA III). Patient demographics were similar in the placebo (n=316) and IV PCA morphine (n=320) treatment groups.

In the pharmacokinetic studies in healthy normal volunteers (n=340), opioid effects were blocked with naltrexone. Of the 340 healthy subjects, 263 were treated with the commercial formulation. The majority of these subjects were male (72.2%) and between the ages of 18 to 39 years (76.0%). There were 29 (11.0%) subjects who were 65 to 84 years of age. Most of the subjects were Caucasians (75.7%), followed by Blacks (17.9%). Mean body weight for all subjects using the commercial formulation was 74.9 kg (range 47.6 to 119.1 kg).

The **extent of exposure** for patients using IONSYS (fentanyl HCl) 40 µg system in controlled trials is given in Table IV.2.4.

Table IV.2.4 Extent of exposure for patients using IONSYS (fentanyl HCl) 40 µg (controlled trials)

| Duration of exposure to study medication (h) | E-TRANS (fentanyl HCl) 40 µg[a] | |
|---|---|---|
| | Mean estimated number of doses/patient (range) | Estimated amount of fentanyl delivered[b] |
| <3<br>n=27 | 7.0<br>(0 – 13) | 280 µg |
| ≥3 – 24<br>n=467 | 29.9<br>(0 – 88) | 1196 µg |
| >24 – ≤48<br>n=211 | 43.4<br>(0 – 163) | 1736 µg |
| >48 – ≤72<br>n=72 | 76.3<br>(13 – 208) | 3052 µg |
| >72<br>n=14 | 81.2<br>(28 – 208) | 3248 µg |
| Total<br>n=791 | 37.8<br>(0 – 208) | 1512 µg |

[a] Six doses available per hour, maximum of 80 doses per 24 hours (unless a second system was required)

[b] Estimated amount of fentanyl delivered = mean number of doses × 40 µg fentanyl (based on a nominal 40 µg dose per delivery)

- Adverse events

In the three placebo-controlled trials (C-2001-011, C-2000-008, C-95-016), the most commonly occurring AEs for patients treated with IONSYS (fentanyl HCl) 40 µg (n=475) or placebo (n=316) were nausea (37.9% versus 21.2%), application-site erythema (14.1% versus 2.2%), vomiting (11.8% versus 5.7%), fever (8.6% versus 10.4%), and headache (8.6% versus 6.6%).

| | E-TRANS (fentanyl HCl) 40 µg n=475 | Placebo n=316 |
|---|---|---|
| Number (%) of Patients who Reported AE | | |
| **Body as a Whole** | | |
| Fever | 41 (8.6%) | 33 (10.4%) |
| Headache | 41 (8.6%) | 21 (6.6%) |
| Back Pain | 8 (1.7%) | 11 (3.5%) |
| **Cardiovascular System** | | |
| Hypotension | 11 (2.3%) | 2 (0.6%) |
| **Digestive System** | | |
| Nausea[a] | 180 (37.9%) | 67 (21.2%) |
| Vomiting[a] | 56 (11.8%) | 18 (5.7%) |
| **Haemic and Lymphatic System** | | |
| Anaemia | 16 (3.4%) | 2 (0.6%) |
| **Nervous System** | | |
| Insomnia | 15 (3.2%) | 16 (5.1%) |
| Dizziness | 14 (2.9%) | 4 (1.3%) |
| **Skin System** | | |
| ASR - Erythema | 67 (14.1%) | 7 (2.2%) |
| Pruritus | 29 (6.1%) | 1 (0.3%) |
| **Urogenital System** | | |
| Urinary retention | 13 (2.7%) | 2 (0.6%) |

[a] In addition to those who reported nausea and those who reported vomiting, the event "nausea and vomiting" (unique COSTART term) was reported by 3 patients (0.6%) in the E-TRANS (fentanyl HCl) 40 µg group and 2 patients (0.6%) in the placebo group.



All adverse events reported at ≥ 2 % in placebo-controlled trials are given in the Table IV.3.2.

**Table IV.3.2** All adverse events reported at ≥ 2 % in placebo-controlled trials (studies C-2001-011, C-2000-008, C-95-016)

The incidence of AEs in placebo-controlled trials, such as fever, headache, and insomnia, possibly reflecting post-operative effects, were similar between the two treatment groups. Typical opioid side effects such as nausea, vomiting, dizziness, pruritus, and urinary retention were experienced more with IONSYS (fentanyl HCl) 40 µg than with placebo. However, nausea and vomiting were also reported by a number of placebo patients, suggesting that a substantial amount of nausea and vomiting in the active group was also due to post-operative effects rather than the opioid alone. Since IONSYS (fentanyl HCl) is an iontophoretic drug delivery device, it is expected that ASRs would be reported more frequently by patients using IONSYS (fentanyl HCl) 40 µg compared with those using placebo, which did not deliver ionised drug through the skin. A somewhat higher proportion of patients on IONSYS (fentanyl HCl) 40 µg reported anaemia relative to those on placebo (3.7% versus 0.6%, respectively). None of the reports of anaemia were assessed as related to study medication.

In the active-controlled study (C-2000-007) with IONSYS (fentanyl HCl) 40 µg (n=316) and IV PCA morphine (n=320), nausea (44.0% versus 49.1%), fever (20.9% versus 20.3%), headache (14.9% versus 9.1%), and vomiting (11.1% versus 9.4%) were also the most commonly occurring AEs. In this study, most of the AEs reported in ≥2% of patients were comparable between the two treatment groups. Headache, constipation, and hypertension were reported at a higher incidence with IONSYS (fentanyl HCl) 40 µg than with IV PCA morphine. Conversely, a higher proportion of patients reported peripheral oedema and pruritus with IV PCA morphine relative to IONSYS (fentanyl HCl) 40 µg. The adverse event profile of the active controlled study is presented below in Table IV.3.3.

**Table IV.3.3** All adverse events reported at ≥ 2 % in IV PCA morphine active-controlled study (C-2000-007)

| | E-TRANS (fentanyl HCl) 40 µg n=316 | IV PCA Morphine n=320 |
|---|---|---|
| Number (%) of Patients who Reported AE | | |
| **Body as a Whole** | | |
| Fever | 66 (20.9%) | 65 (20.3%) |
| Headache | 47 (14.9%) | 29 (9.1%) |
| Abdominal Pain | 9 (2.8%) | 12 (3.8%) |
| **Cardiovascular System** | | |
| Hypotension | 7 (2.2%) | 7 (2.2%) |
| Hypertension | 7 (2.2%) | 3 (0.9%) |
| Tachycardia | 4 (1.3%) | 9 (2.8%) |
| **Digestive System** | | |
| Nausea[a] | 139 (44.0%) | 157 (49.1%) |
| Vomiting[a] | 35 (11.1%) | 30 (9.4%) |
| Constipation | 14 (4.4%) | 9 (2.8%) |
| Flatulence | 9 (2.8%) | 8 (2.5%) |
| **Haemic and Lymphatic System** | | |
| Anaemia | 13 (4.1%) | 15 (4.7%) |
| Peripheral Oedema | 3 (0.9%) | 12 (3.8%) |
| **Nervous System** | | |
| Dizziness | 11 (3.5%) | 13 (4.1%) |
| Anxiety | 8 (2.5%) | 11 (3.4%) |
| Somnolence | 9 (2.8%) | 8 (2.5%) |
| **Respiratory System** | | |
| Hypoxia | 13 (4.1%) | 11 (3.4%) |
| Pharyngitis | 8 (2.5%) | 5 (1.6%) |
| **Skin System** | | |
| ASR- Erythema | 7 (2.2%) | 0 |
| ASR- Itching | 7 (2.2%) | 0 |
| Injection Site Reaction | 9 (2.8%) | 7 (2.2%) |
| Pruritus | 26 (8.2%) | 40 (12.5%) |

[a] In addition to those who reported nausea and those who reported vomiting, the event "nausea and vomiting" (unique COSTART term) was reported by 2 patients (0.6%) in the E-TRANS (fentanyl HCl) 40 µg group and 4 patients (1.3%) in the IV PCA morphine group.

The erythema presented by 48.3 % patients in controlled studies was generally mild. It seems that it was mainly resolved without treatment.

Due to the open-label study design in study C-2000-007 a valid comparison between the safety profile of IONSYS (fentanyl HCl) 40 µg and IV PCA morphine is difficult.

In the controlled studies, the majority of AEs reported were mild or moderate in severity and were considered treatment-related. Of the commonly reported AEs (nausea, fever, headache, vomiting, pruritus, and Application site reactions (ASR)-erythema), only fever was judged as predominantly not treatment-related. Nausea, headache, vomiting, and pruritus were mostly judged as treatment-related by the investigator and across all three treatment groups were mostly of mild severity All reports of ASR-erythema were considered treatment-related. The erythema was of mild severity in 10.4% of patients, of moderate severity in 5.1%, and severe in 0.6%, and mostly resolved without treatment.

In the controlled clinical trials, a comparable patient percentage had an adverse event related to study medication via IONSYS (fentanyl HCl) 40 µg (55.9%, 442/791) compared with IV PCA morphine (63.4%, 203/320). A lower percentage of patients in the placebo group had an adverse event that was considered related to treatment (32.9%, 104/316). In the controlled clinical studies, a comparable patient percentage had an adverse event related to study medication via IONSYS (fentanyl HCl) 40 µg (55.9%,442/791) compared with IV PCA morphine (63.4%, 203/320). A lower percentage of patients in the placebo group had an adverse event that was considered related to treatment (32.9%, 104/316).

The incidence of typical opioid side effects related to treatment with IONSYS (fentanyl HCl) 40 µg in the controlled studies was similar to the safety data on post-operative opioid associated AEs in literature. During the IONSYS (fentanyl HCl) clinical development programme, there were no deaths due to an excess of opioids.

Of the 2,660 patients in all clinical studies, there was only one instance of clinically relevant respiratory depression (CRRD), and it occurred in one patient treated with IV PCA morphine in study C-2000-007. Of the 1142 patients who were treated with IONSYS (fentanyl HCl) 40 µg in all clinical studies, very few patients had symptoms of respiratory depression reported: 30 (2.6%) hypoxia, 5 (0.4%) hypoventilation, and 6 (0.5%) apnoea.

To further evaluate respiratory depression the following AEs, which could be suggestive of respiratory or CNS depression, were analysed in the controlled studies: hypoxia, hypoventilation, apnoea, somnolence, and confusion. Post-enrolment vital signs were also reviewed to identify patients in the controlled studies who had at least one respiratory rate (RR) <8 bpm or oxygen saturation ($SpO_2$) <90%. This review included patients regardless of AE relationship to study drug and regardless of whether the vital sign finding, isolated or not, resulted in any symptoms or was clinically significant. The summary of respiratory and CNS effects (AEs and vital signs) from controlled trials is given in Table IV.3.8.

**Table IV.3.8 The summary of respiratory and CNS effects (AEs and vital signs) from controlled trials**

| | E-TRANS (fentanyl HCl) 40 µg n=791 | IV PCA morphine n=320 | Placebo n=316 |
|---|---|---|---|
| Selected AEs[a] | 44 (5.6%) | 25 (7.8%) | 2 (0.6%) |
| Selected Vital Signs[b] | 18 (2.3%) | 13 (4.1%) | 3 (0.9%) |
| Total | 62 (7.8%) | 38 (11.9%) | 5 (1.6%) |

[a] Hypoxia, hypoventilation, apnoea, somnolence, and confusion

[b] One RR <8 bpm or one $SpO_2$ <90% without selected AEs

A lower proportion of patients who reported AEs that could be suggestive of respiratory or CNS depression was observed in the placebo group (0.6%) compared with the active treatment groups. In the IONSYS (fentanyl HCl) 40 µg group 5.6 % of patients reported these selected AEs. The selected AEs were reported by 7.8 % of patients in the IV PCA morphine group.

- Serious adverse event/deaths/other significant events

No deaths occurred with IONSYS (fentanyl HCl) 40 µg treatment during a clinical study.

Forty-eight (4.2%) of the 1142 patients using IONSYS (fentanyl HCl) 40 µg developed a Serious adverse event (SAE). A similar percentage of patients in the placebo and IV PCA morphine groups had an SAE, 3.7% (12/321) and 3.6% (13/361), respectively. All serious adverse events related to the study medication in treated patients are summarised in Table IV.4.1.

Table IV.4.1 All serious adverse events related to the study medication in treated patients

| | Treatment Group | | | | | |
|---|---|---|---|---|---|---|
| | E-TRANS (fentanyl (HCl) | | | | IV PCA | IM |
| | 25 µg (n=765) | 40 µg (n=1142) | 25/40 µg (n=28) | Placebo (n=321) | (morphine) (n=361) | (morphine) (n=43) |
| **Number (%) of patients with** no serious adverse events related to study medication | 763 (99.7%) | 1137 (99.6%) | 28 (100.0%) | 321 (100.0%) | 360 (99.7%) | 43 (100.0%) |
| at least one serious adverse event related to study medication | 2 (0.3%) | 5 (0.4%) | 0 | 0 | 1 (0.3%) | 0 |
| **Number (%) of patients who reported adverse events by body system[a]** | | | | | | |
| Digestive system | 1 (0.1%) | 4 (0.4%) | 0 | 0 | 0 | 0 |
| Ileus | 1 (0.1%) | 3 (0.3%) | 0 | 0 | 0 | 0 |
| Nausea | 0 | 1 (0.1%) | 0 | 0 | 0 | 0 |
| Vomiting | 0 | 1 (0.1%) | 0 | 0 | 0 | 0 |
| Nervous system | 1 (0.1%) | 1 (0.1%) | 0 | 0 | 1 (0.3%) | 0 |
| Somnolence | 1 (0.1%) | 0 | 0 | 0 | 1 (0.3%) | 0 |
| Confusion | 0 | 1 (0.1%) | 0 | 0 | 0 | 0 |
| Respiratory system | 0 | 0 | 0 | 0 | 1 (0.3%) | 0 |
| Hypoventilation | 0 | 0 | 0 | 0 | 1 (0.3%) | 0 |

Five of the patients using IONSYS (fentanyl HCl) 40 µg had SAEs that were judged related to study medication by the investigator: confusion (1), nausea and vomiting(1), ileus (3). None of these related SAEs were respiratory system events.

The overall incidence of serious adverse events in treated patients was low and does not allow concluding that the SAE profile of these patients is different from the profile with PCA opioid use in general.

- Laboratory findings

The clinical laboratory evaluations were the standard clinical laboratory tests (haematology, clinical chemistry and urinalysis). The deviations in vital signs are considered minor.

- Safety in special populations

The impact of age, gender, race, surgery type, history of renal or hepatic dysfunction on the IONSYS (fentanyl HCl) 40 µg safety profile was investigated.

*Elderly:*
No overall differences in AE's were observed in patients over 65 years (including a subset over 75 years) and adult patients for all studies and all controlled studies.

*Paediatrics*
At least one AE was reported by paediatric patients. Nausea, vomiting, fever and headache were the most common. Vomiting and fever were each reported by a higher percentage of paediatric patients relative to adults. Most of these reports were not judged to be due to study medication. and none resulted in discontinuation of study medication.

*History of renal or hepatic dysfunction*
AE's reported by these patients were similar to those reported overall with nausea, fever, headache, application skin site erythema and vomiting being most frequently reported.

*Pregnancy and lactation*
No pregnancies were reported during the clinical trial programme. However the safe use of fentanyl has not been estableished with respect to possible adverse effects on foetal development andf E_TRANS should only be used in pregnancy if potential benefit outweighs the risk to the foetus. Nursing is not recommended for 24 hours following removal of E-TRANS.

- Safety related to drug-drug interactions, other interactions and overdose/misuse/abuse

*Drug interactions*
No formal drug interaction clinical studies have been conducted. However a review of the database showed that 96% of patients received other opiates, sedative -hypnotics, tranquilisers, antihistamines, phenothiazines and other potentially sedating medications. No patients experienced clinically relevant respiratory depression. However the concomitant use of other CNS depressants may produce additive depressant effects. Therefore the use of these drugs with E-TRANS Fentanyl HCL requires special patient care and observation.

27% of patients received CYP3A4 inhibitors or inducers of fentanyl metabolism. There were no substantial differences in the incidence of nausea, vomiting, headache, pruritus, apnoea, hypoxia, hypoventilation, somnolence or confusion relative to all patients.

Based on the in-vitro study (see Appendix 2) the concomitant use of ritonavir and ketoconazole is not recommended unless the patient is closely monitored.

*Overdose:*
There appears to be no evidence of increased respiratory depression with patient controlled anaesthesia than with other modes of opioid administration. The risk of overdose with E-TRANS is expected to be less than that for IV PCA due to the system: self administration should limit the possibility of overdose as the patient will become drowsy or sleepy and will stop pushing the button for additional doses before an overdose could occur.
In addition the applicant highlights several features of the system that will minimise the potential; for overdose, including a lockout system for a maximum of 6 doses per hour and practical design mechanisms for minimising inadvertent dose activation.

*Potential for overdose in infants and small children:*
No new safety issues beyond those associated with administration of opioids to adults were identified. However safety was not studied in children and adolescents and the proposed indication is for use in adult patients only. The product will be dispensed in child resistant packaging, and will be recommended for use in medically supervised settings only.
If a child does ingest a system there is a high risk of fatal overdose.

*Potential for abuse and misuse of E-TRANS:*
The applicant has undertaken a risk analysis of this eventuality and specific measures are described in the risk management plan.

Of 1907 patients in clinical studies who used an IONSYS (fentanyl HCl) system (40 µg [n=1142] or 25 µg [n=765]), there was no evidence of intentional abuse of the system and no cases of system malfunction resulting in an overdose situation.
There were 3 instances of misuse of misuse that involved a family member pressing the dosing button. 1 patient suffered hypoxia which resolved within 40 minutes of administration and the other suffered somnolence for 8 hours after removal of the system.

As regards deliberate abuse the SPC contains the warning 'Oral ingestion of the fentanyl containing hydrogel may cause life threatening hypoventilation or death. Do not touch hydrogel with fingers or allow hydrogel to touch mouth.'

Because IONSYS (fentanyl HCl) 40 µg will be indicated for the treatment of acute pain, physical dependence, which is quite common after use of opioids for periods of more than 10-20 days, is

unlikely to be an issue with IONSYS (fentanyl HCl) use. No opiate withdrawal symptoms were observed in IONSYS (fentanyl HCl) clinical studies. Similarly, in short-term pain, which is the indication for IONSYS (fentanyl HCl), there is little risk of rebound as the pain is self-limiting.

- Discontinuation due to adverse events

The percentage of patients who discontinued due to adverse events was low, therefore no specific signal or trend could be observed. The reasons given for discontinuation represent the typical opioid side effects and the patient's post-operative status in the studied population. The pediatric database is too small to draw any conclusions on discontinuations and is not relevant for the current application.

- Post marketing experience

N/A

- Discussion on clinical safety

The AE profile of the product in the studied population regarding the typical opioid undesirable effects is considered similar to the postoperative opioid use AE profile published in literature. There is no unexpected safety issue in the most important undesirable effect, respiratory depression in this population. The overall number of deaths reported among treated patients is consistent with what might be expected in such postoperative patients as the ones studied in these trials irrespective of their pain management. The overall incidence of serious adverse events in treated patients was low and does not allow to conclude that the SAE profile of these patients is different from the profile with PCA opioid use in general. The low number of patients with ASA physical status higher than II, elderly patients and obese patients have been addressed by including statements in the SPC regarding the lack of data these populations of patients.

The erythema presented by 48.3 % patients in controlled studies was generally mild. It seems that it was mainly resolved without treatment.

The number of old and very old patients is relatively small, and this lack of data is reflected in the SPC. Post-operative nausea and vomiting usually affects younger patients and females more than elderly patients and males, so the results for these adverse events are not unexpected. The safety analysis in elderly patients is focused on nausea, vomiting, fever and headache. Nervous system, respiratory and cardiovascular system events all occurred slightly more frequently in the elderly (over 64 years), as would be expected.

In the elderly, although there was a slightly overall higher incidence of cardiovascular events in E-TRANS relative to IV PCA morphine in the elderly, the incidence of CV AEs of moderate severity or greater are similar between the two treatment groups. The incidence of confusion related to study medication in E-TRANS (1.1%, 2/186) and IV PCA morphine (1.6%, 1/ 62) were similar with none in the placebo group. There was no report of hallucination in elderly patients in any of these three treatment groups. In the evaluation of all treated patients (controlled studies), the incidence of confusion was identical (0.3%) in all three treatment groups: 2/ 791 in E-TRANS, 1/320 in IV PCA, and 1/316 in placebo. The incidence of hallucination was 0.3% (2/791) in E-TRANs and 0 in IV PCA morphine and placebo. Both cases of hallucination were reported as mild in severity in E-TRANS patients under age 65.

The safety data in paediatric patients is insufficient for assessment and it is not relevant for the current application.

The warning in SPC concerning the need for careful observation when patients with hepatic and renal impairment are is considered adequate. The recommendation of not to use the product in pregnancy and lactation is considered adequate.

The applicant's conclusions regarding the potential drug-drug interaction are endorsed. In the SPC, a warning for concomitant use of other CNS depressants is considered adequate. Warning regarding the concomitant use of the product with potent CYP3A4 inhibitors are included in section 4.4 with cross reference to 4.5. As the IONSYS (fentanyl HCl) system delivers a fixed dose of fentanyl, the patients are clearly informed how to use the product if the concomitant use of CNS depressants and CYP3A4 inhibitors is required.

The percentage of patients who discontinued due to adverse events was low, therefore no specific signal or trend could be observed. The reasons given for discontinuation represent the typical opioid undesirable effects and the patient's post-operative status in the studied population.

External heaters are frequently used in the post-operative patient care. The applicant's comment explaining that no significant effect of post-operative external heaters is expected on the safety of the product was endorsed.

A potentially lethal amount of fentanyl remains in the IONSYS system after use and there is potential for abuse of the remaining fentanyl in the used system. A warning for oral ingestion of the hydrogel is included in the SPC. This information is also clearly described to the prescriber and the patient. Use of IONSYS must be restricted to medically supervised setting. There is also clear information for dispose of the used product since which should be done by medical staff only.



### 1.5 Description of the Pharmacovigilance system

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided. .

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

### 1.6 Risk Management Plan

The company has submitted comprehensive risk management and post-marketing pharmacovigilance plans to address the specific opioid PCA related issues. These include overdose, underdose, accidental exposure, misuse and abuse, mechanical failures, and use in patients with drug.

*Product specific surveillance*
In addition to routine pharmacovigilance surveillance, product-specific surveillance activities will be performed to address AEs of special interest. The product-specific surveillance plan is a comprehensive program utilizing multiple databases from different sources, each of which was selected based on the capability to detect, characterize and monitor over time the identified key safety risks associated with IONSYS™. The objectives are to monitor the following AEs: overdose, death, abuse, addiction or misuse (use inconsistent with labeling whether intentional or unintentional), misuse by health care providers, reports suggesting diversion, medication errors, and respiratory depression.

*Risks minimisation plan*
As a number of potential and actual risks have been identified, a risk minimisation plan is proposed by the applicant. The minimisation system includes and takes into account that:

- Fentanyl is a substance in Schedule I of the UN convention of 1961 on narcotics, subject to specific legal measures in the EU Member States
- The use is restricted in hospital and arrangements for disposal are made.
- A controlled distribution system direct from the manufacturer will be in place

- System designed to reduce the misuse and packaging is child-resistant

*Education material*

The applicant should provide and the Member States must ensure that the education plans for health care professionals and patients contains measures to minimise the risks relative to overdose/ underdose, accidental exposure, misuse/abuse/diversion, mechanical failures, use in patients with a history of drug abuse, and disposal according to the local legal requirements
There will be an education program for health care professionals on launch of the product. Training will be provided to Physicians, Nurses and Pharmacists prior to the use of IONSYS. These may include, but not be limited to representative in-services, videos, web casts, CD/ROMs, demonstration units and printed brochures. Physician and nurse training will focus on the appropriate use of IONSYS. Brochures devoted to pharmacists will concentrate on system testing and proper disposal. All materials will include a phone number to a dedicated call centre setup to handle medical questions. Non-drug containing, demo systems will be in place to ensure hospitals without prior experience with IONSYS will be trained. When a Hospital places it's first order, the supply chain will notify the Company of the training requirement.

Training for the patients will be via a healthcare professional. Training information will include, but will not be limited to description of the safe use of IONSYS, when it is appropriate to initiate a dose, explanation of alarms, placement on the body, communication that only the patient should administer a the dose and that the system should be worn at all times.

### 1.7 Overall conclusions, benefit/risk assessment and recommendation

**Quality**

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

**Non-clinical pharmacology and toxicology**

Non-clinical data generated to support previous applications for fentanyl-containing products have been reviewed by the applicant. The pharmacodynamics and safety pharmacology of fentanyl are well characterised.
The non-clinical development programme has appropriately concentrated on studies specifically relating to the new mode of delivery and to the components of the IONSYS system.

The applicant adequately quantified the flux of fentanyl across the skin from the IONSYS unit. There were no unexpected findings.

Results of repeated dose toxicity studies and mutagenicity/clastogenicity tests do not raise specific concern over carcinogenic potential.

Altogether, a comprehensive programme of local tolerance and sensitisation studies have been carried out. The results show a mild to moderate skin irritation and sensitisation potential.

As a strong opioid, fentanyl has the potential to induce dependence. This has been addressed in the review of pharmacodynamic properties. Since the medicinal product is intended for use in a medically supervised setting and indicated only for the short term management of postoperative pain, there are no specific concerns related to dependence potential of this medicinal product.

**Efficacy**
The clinical programme comprised two dose-finding studies, four uncontrolled studies and four controlled Phase III studies. The Phase III studies comprised one small, single-centre study, two larger placebo-controlled trials and an active-control, non-inferiority trial.

In both placebo-controlled studies, the primary objective was to assess the effect of E-TRANS in patients who were 'comfortable'. This was assessed using the population of patients that continued with treatment for longer that the first 3 hours in which supplemental analgesics were permitted. This complicates the interpretation of these studies, firstly because this is a subgroup of all randomised patients and secondly because of potential imbalances brought about by differential numbers of withdrawals between the treatment groups. The 'all-treated-patients' analysis, which was conducted as a secondary analysis, is preferred. This latter analysis provides adequate evidence of a benefit for E-TRANS over placebo, with the proportion of patients withdrawing due to inadequate pain control being 31.2% on E-TRANS and 45.1% on placebo ($p=0.07$) in one study and 28.7% on E-TRANS and 60% on placebo ($p<0.0001$) in the second study.

The small single-centre study provided supportive evidence of efficacy.

In the active-controlled study, non-inferiority was not considered to be demonstrated. Therefore, the SPC includes a no claim of similar efficacy between IONSYS and IV PCA morphine .

The remaining issue was to provide data on time to pain relief to demonstrate that the risk of overdose by self titration is not clinically significant. The applicant committed to provide a clinical study as a follow-up measure.

**Safety**

The system appeared to be well tolerated in 1142 post-operative patients for up to 74 hours. No unexpected safety issues were identified other than the known expected issues with other fentanyl dose forms. In particular, no clinically significant respiratory depression was observed.

There were 3 deaths in the development programme, none being related to study medication. A total of 4.2% of patients reported at least one serious adverse event. Few of these events were related to study medication: confusion (1), nausea and vomiting (1 case each in the same patient) and ileus. Nausea, fever and vomiting and pruritus were the most commonly reported AE's and most were mild. Somnolence, hypoxia and dyspnoea were reported infrequently. Increased usage (greater than 60 doses in 24 hours) led to more reports of opioid side effects. The system was well tolerated in elderly patients. System application was well tolerated at skin sites. Erythema at the application site was mostly mild and self limiting, with no treatment required.

The evidence of safety is acceptable.

Since IONSYS is indicated only for a short-term treatment the risks related to the dependence potential are not of concern. There was also no evidence of abuse of the system during the clinical trials.

A potentially dangerous amount of fentanyl remains in the IONSYS system after use. This information is clearly described to the prescriber and the patient. Use of IONSYS must be restricted to medically supervised setting. Also, disposal of IONSYS should be done by medical staff through specific arrangements (follow-up measures).

**Risk management plan**

In addition to routine pharmacovigilance surveillance, product-specific surveillance activities will be performed to address AEs of special interest. The product-specific surveillance plan is a comprehensive program utilizing multiple databases from different sources, each of which was selected based on the capability to detect, characterize and monitor over time the identified key safety

risks associated with IONSYS™. The objectives are to monitor the following AEs: overdose, death, abuse, addiction or misuse (use inconsistent with labelling whether intentional or unintentional), misuse in health care providers, reports suggesting diversion, medication errors, and respiratory depression.

The applicant will provide an educational plan for patients, physicians and health care providers, which is aimed at risk minimisation and to support safe and effective use for the product

Furthermore, the applicant committed to provide a proposal for a methodology to assess the effectiveness of risk minimisation measures across the EU, including milestones for such assessment. This should be in line with the CHMP Guideline on Risk Management Systems for Medicinal Products for Human use and should be submitted within 30 days after the Commission Decision. The RMP should be updated as recommended in the CHMP Guideline on Risk Management Systems for Medicinal Products for Human use, and submitted at the same time as PSURs, when new information is received, within 60 days of an important milestones being reached or the results of a study becoming available (see follow-up measures timeline), and upon request of a Competent authority.

**Benefit/risk assessment**

IONSYS is a non-invasive, needle-free, preprogrammed, transdermal PCA system using iontophoresis for delivery of fentanyl, offering potential benefits compared to IV PCA..

CPMP Scientific Advice was requested by the applicant with regards to clinical development of IONSYS. The applicant did not follow all aspects of the advice., however all the concerns raised by the CHMP have been solved.

With regards to efficacy, the remain issue was to provide data on time to pain relief to demonstrate that the risk of overdose by self titration is not clinically significant. The applicant committed to provide a clinical study as a follow-up measure.

With regards to safety, the Adverse Effect profile of the product in the studied population regarding the typical opioid undesirable effects is considered similar to the postoperative opioid use AE profile published in literature. There is no unexpected safety issue in the most important undesirable effect, respiratory depression in this population.

As fentanyl is a controlled narcotic substance, it will be subject to a special medical prescription

A potentially dangerous amount of fentanyl remains in the IONSYS system after use. This information is clearly described to the prescriber and the patient. Use of IONSYS must be restricted to medically supervised setting resulting in its being subject to restricted medical prescription. Also, disposal of IONSYS should be done by medical staff through specific arrangements (follow-up measures).

The applicant has also committed to provide a pediatric development plan for IONSYS (fentanyl HCl) and to conduct PK and safety studies in children.

The risk management plan and the evaluation of the effectiveness of the minimisation strategies will be updated regularly according to the CHMP Guideline on Risk Management Systems for Medicinal Products for Human use.

**Recommendation**

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered that the benefit/risk ratio of Ionsys in "the management of acute moderate to severe post-operative pain for use in a hospital setting only" was favourable and therefore recommended the granting of the marketing authorisation