SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Victanyl 12 micrograms/hour Transdermal Patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Victanyl 12 micrograms/h transdermal patch

Each patch releases 12.5 micrograms fentanyl per hour. Each patch of 4.25 cm2 contains 2.55 mg fentanyl.

Excipient with known effect

Aloe vera leaf extract oil (on the basis of soya oil tocopherol acetate)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch

Each patch: Opaque and colourless rectangular shaped patch with round corners and imprint on the backing foil:

“Fentanyl 12µg/h”.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults

Victanyl is indicated for management of severe chronic pain that requires continuous long term opioid administration.

Children

Long term management of severe chronic pain in children from 2 years of age who are receiving opioid therapy.

4.2 Posology and method of administration

Prior to starting treatment with opioids, a discussion should be held with patients to put in place a strategy for ending treatment with fentanyl in order to minimise the risk of addiction and drug withdrawal syndrome (see section 4.4).

Posology
Victanyl doses should be individualised based upon the status of the patient and should be assessed at regular intervals after application. The lowest effective dose should be used. The patch is designed to deliver approximately 12 mcg/h fentanyl to the systemic circulation, which represent about 0.3 mg per day respectively.

Initial dosage selection
The appropriate initiating dose of Victanyl should be based on the patient's current opioid use. It is recommended that Victanyl be used in patients who have demonstrated opioid tolerance. Other factors to be considered are the current general condition and medical status of the patient, including body size, age, and extent of debilitation as well as degree of opioid tolerance.

Adults:
Opioid-tolerant patients
To convert opioid-tolerant patients from oral or parenteral opioids to Victanyl refer to *Equianalgesic potency conversion* below. The dosage may subsequently be titrated upwards or downwards, if required, in increments of either 12 or 25 mcg/hr to achieve the lowest appropriate dose of Victanyl depending on the response and supplementary analgesic requirements.

Opioid-naive patients
Generally, the transdermal route is not recommended in opioid-naïve patients. Alternative routes of administration (oral, parenteral) should be considered. To prevent overdose it is recommended that opioid-naïve patients receive low doses of immediate-release opioids (eg, morphine, hydromorphone, oxycodone, tramadol and codeine) that are to be titrated until an analgesic dosage equivalent to transdermal fentanyl with a release rate of 12 mcg/h or 25 mcg/h is attained. Patients can then switch to Victanyl. Patches with a release rate of 25, 50, 75 and 100 mcg/h are available.

In the circumstance in which commencing with oral opioids is not considered possible and transdermal fentanyl is considered to be the only appropriate treatment option for opioid-naïve patients, only the lowest starting dose (ie, 12 mcg/h) should be considered. In such circumstances, the patient must be closely monitored. The potential for serious or life-threatening hypoventilation exists even if the lowest dose of transdermal fentanyl is used in initiating therapy in opioid-naïve patients (see sections 4.4 and 4.9).

Equianalgesic potency conversion

In patients currently taking opioid analgesics, the starting dose of Victanyl should be based on the daily dose of the prior opioid. To calculate the appropriate starting dose of Victanyl follow the steps below.

1. Calculate the 24-hour dose (mg/day) of the opioid currently being used.
2. Convert this amount to the equianalgesic 24-hour oral morphine dose using the multiplication factors in Table 1 for the appropriate route of administration. .
3. To derive the Victanyl dosage corresponding to the calculated 24-hour, equianalgesic morphine dosage, use dosage-conversion Table 2 or 3 as follows:
    a. **Table 2** is for adult patients who have a need for opioid rotation or who are less clinically stable (conversion ratio of oral morphine to transdermal fentanyl approximately equal to 150:1).
    b. **Table 3** is for adult patients who are on a stable and well-tolerated opioid regimen (conversion ratio of oral morphine to transdermal fentanyl approximately equal to 100:1).

Table 1: Conversion Table - Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Equianalgesic 24-hour ***Oral*** Morphine Dose
(mg/day Prior Opioid x Factor = Equianalgesic 24-hour oral Morphine Dose)

Prior Opioid	Route of Administration	Multiplication Factor
morphine	oral	1[a]
	parenteral	3
buprenorphine	sublingual	75
	parenteral	100
codeine	oral	0.15
	parenteral	0.23[b]
diamorphine	oral	0.5
	parenteral	6[b]
fentanyl	oral	-
	parenteral	300
hydromorphone	oral	4
	parenteral	20[b]
ketobemidone	oral	1
	parenteral	3
levorphanol	oral	7.5
	parenteral	15[b]
methadone	oral	1.5
	parenteral	3[b]
oxycodone	oral	1.5
	parenteral	3
Oxymorphone	rectal	3
	parenteral	30[b]
Pethidine	oral	-
	parenteral	0.4[b]
Tapentadol	oral	0.4
	parenteral	-
Tramadol	oral	0.25
	parenteral	0.3

[a] The oral/IM potency for morphine is based on clinical experience in patients with chronic pain.

[b]Based on single-dose studies in which an IM dose of each active substance listed was compared with morphine to establish the relative potency. Oral doses are those recommended when changing from a parenteral to an oral route.

Reference: Adapted from 1) Foley KM. The treatment of cancer pain. NEJM 1985; 313 (2): 84-95, and 2) McPherson ML. Introduction to opioid conversion calculations. In: Demystifying Opioid Conversion Calculations: A Guide for Effective Dosing. Bethesda, MD: American Society of Health- System Pharmacists; 2010:1-15.

Table 2: Recommended starting dosage of transdermal fentanyl based upon daily oral morphine dose (for patients who have a need for opioid rotation or for clinically less stable patients: conversion ratio of oral morphine to transdermal fentanyl is approximately equal to 150:1)[1]

Oral 24-hour morphine (mg/day)	***Transdermal fentanyl Dosage (mcg/hr)***
< 90	*12*
90-134	*25*
135-224	*50*
225-314	*75*
315-404	*100*
405-494	*125*
495-584	*150*
585-674	*175*
675-764	*200*
765-854	*225*
855-944	*250*
945-1034	*275*
1035-1124	*300*

[1] *In clinical studies these ranges of daily oral morphine doses were used as a basis for conversion to transdermal fentanyl.*

Table 3: Recommended starting dosage of transdermal fentanyl based upon daily oral morphine dosage (for patients on stable and well tolerated opioid therapy: conversion ratio of oral morphine to transdermal fentanyl is approximately equal to 100:1**)**

Oral 24-hour morphine (mg/day)	*Transdermal fentanyl Dosage (mcg/hr)*
≤ 44	*12*
45-89	*25*
90-149	*50*
150-209	*75*
210-269	*100*
270-329	*125*
330-389	*150*
390-449	*175*
450-509	*200*
510-569	*225*
570-629	*250*
630-689	*275*
690-749	*300*

Initial evaluation of the maximum analgesic effect of Victanyl cannot be made before the patch is worn for 24 hours. This delay is due to the gradual increase in serum fentanyl concentration in the 24 hours following initial patch application.

Previous analgesic therapy should therefore be gradually phased out after the initial dose application until analgesic efficacy with Victanyl is attained.

Dose titration and maintenance therapy
The Victanyl patch should be replaced every 72 hours.

The dose should be titrated individually on the basis of average daily use of supplemental analgesics until a balance between analgesic efficacy and tolerability is attained. Dosage titration should normally be performed in 12 mcg/h or 25 mcg/h increments, although the supplementary analgesic requirements (oral morphine 45/90 mg/day ≈ transdermal fentanyl 12/25 mcg/h) and pain status of the patient should be taken into account. After an increase in dose, it may take up to 6 days for the patient to reach equilibrium on the new dose level. Therefore after a dose increase, patients should wear the higher dose patch through two 72-hour applications before any further increase in dose level is made.

More than one Victanyl patch may be used for doses greater than 100 mcg/h. Patients may require periodic supplemental doses of a short acting analgesic for "breakthrough" pain. Some patients may require additional or alternative methods of opioid administration when the Victanyl dose exceeds 300 mcg/h.

If analgesia is insufficient during the first application only, the Victanyl patch may be replaced after 48 hours with a patch of the same dose, or the dose may be increased after 72 hours.

If the patch needs to be replaced (eg, the patch falls off) before 72 hours, a patch of the same strength should be applied to a different skin site. This may result in increased serum concentrations (see section 5.2) and the patient should be monitored closely.

Discontinuation of Victanyl
If discontinuation of Victanyl is necessary, replacement with other opioids should be gradual, starting at a low dose and increasing slowly. This is because fentanyl concentrations fall gradually after transdermal fentanyl is removed. It may take 20 hours or more for the fentanyl serum concentrations to decrease 50%. In general, the discontinuation of opioid analgesia should be gradual, in order to prevent withdrawal symptoms (see section 4.8).
Opioid withdrawal symptoms are possible in some patients after conversion or dose adjustment.

Table 1, 2 and 3 should only be used to convert from other opioids to transdermal fentanyl and not from transdermal fentanyl to other therapies to avoid overestimating the new analgesic dose and potentially causing overdose.

Special populations

Elderly patients
Elderly patients should be observed carefully and the dose should be individualised based upon the status of the patient (see sections 4.4 and 5.2).

In opioid-naïve elderly patients, treatment should only be considered if the benefits outweigh the risks. In these cases, only Victanyl 12 mcg/h dosage should be considered for initial treatment.

Renal and hepatic impairment
Patients with renal or hepatic impairment should be observed carefully and the dose should be individualised based upon the status of the patient (see sections 4.4 and 5.2).

In opioid-naïve patients with renal or hepatic impairment, treatment should only be considered if the benefits outweigh the risks. In these cases, only Victanyl 12 mcg/h dosage should be considered for initial treatment.

Paediatric population

Children aged 16 years and above
Follow adult dosage

Children 2 to 16 years old
Victanyl should be administered to only those opioid-tolerant paediatric patients (ages 2 to 16 years) who are already receiving at least 30 mg oral morphine equivalents per day. To convert paediatric patients from oral or parenteral opioids to Victanyl refer to Equianalgesic potency conversion (Table 1) and Recommended Victanyl dosage based upon daily oral morphine dose (Table 4).

Table 4: Recommended transdermal fentanyl dosage for paediatric patients[1] based upon daily oral morphine dose[2]

Oral 24-hour morphine (mg/day)	Transdermal fentanyl Dosage (mcg/h)
30-44	12
45-134	25

[1] Conversion to transdermal fentanyl dosages greater than 25 mcg/h is the same for paediatric patients as it is for adult patients (see table 2).
[2] In clinical studies these ranges of daily oral morphine doses were used as a basis for conversion to fentanyl transdermal patches.

In two paediatric studies, the required fentanyl transdermal patch dose was calculated conservatively: 30 mg to 44 mg oral morphine per day or its equivalent opioid dose was replaced by one transdermal fentanyl 12 mcg/h patch. It should be noted that this conversion schedule for children only applies to the switch from oral morphine (or its equivalent) to fentanyl patches. The conversion schedule should not be used to convert from transdermal fentanyl into other opioids, as overdosing could then occur.

The analgesic effect of the first dose of Victanyl patches will not be optimal within the first 24 hours. Therefore, during the first 12 hours after switching to Victanyl, the patient should be given the previous regular dose of analgesics. In the next 12 hours, these analgesics should be provided based on clinical need.

Monitoring of the patient for adverse events, which may include hypoventilation, is recommended for at least 48 hours after initiation of Victanyl therapy or up-titration of the dose (see section 4.4).

Victanyl should not be used in children aged less than 2 years because the safety and efficacy have not been established.

Dose titration and maintenance in children
The Victanyl patch should be replaced every 72 hours. The dose should be titrated individually until a balance between analgesic efficacy and tolerability is attained.

Dosage must not be increased in intervals of less than 72 hours. If the analgesic effect of Victanyl is insufficient, supplementary morphine or another short-duration opioid should be administered. Depending on the additional analgesic needs and the pain status of the child, it may be decided to increase the dose. Dose adjustments should be done in 12 mcg/h steps.

Method of administration

Victanyl is for transdermal use.

Victanyl should be applied to non-irritated and non-irradiated skin on a flat surface of the torso or upper arms.

In young children, the upper back is the preferred location, to minimize the potential of the child removing the patch.

Hair at the application site (a non-hairy area is preferable) should be clipped (not shaved) prior to application. If the site of Victanyl application requires cleansing prior to application of the patch, this should be done with clear water. Soaps, oils, lotions, or any other agent that might irritate the skin or alter its characteristics should not be used. The skin should be completely dry before the patch is applied. Patches should be inspected prior to use. Patches that are cut, divided, or damaged in any way should not be used.

Victanyl should be applied immediately upon removal from the sealed package. The release liner for the patch is slit. Fold the patch in the middle and remove each half of the liner separately. Avoid touching the adhesive side of the patch. Apply the patch to the skin by applying light pressure with the palm of the hand for about 30 seconds. Make certain that the edges of the patch are adhering properly. Then wash hands with clean water.

Victanyl may be worn continuously for 72 hours. A new patch should be applied to a different skin site after removal of the previous transdermal patch. Several days should elapse before a new patch is applied to the same area of the skin.

As the transdermal patch is protected by an outer waterproof backing film, it can also be worn while showering.

Occasionally, additional adhesion of the patch may be required.

If traces of the transdermal patch remain on the skin after its removal, these can be cleaned off using copious amounts of soap and cool water. No alcohol or other solvents may be used for cleaning, as these may penetrate the skin due to the effect of the patch.

4.3 Contraindications

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

Acute or postoperative pain, because there is no opportunity for dose titration during short-term use and because serious or life-threatening hypoventilation could result.

Severe respiratory depression.

Contraindicated in opioid naïve patients.

4.4 Special warnings and precautions for use

Patients who have experienced serious adverse events should be monitored for at least 24 hours after removal of Victanyl or more, as clinical symptoms dictate, because serum fentanyl concentrations decline gradually and are reduced by about 50% 20 to 27 hours later.

Patients and their carers must be instructed that Victanyl contains an active substance in an amount that can be fatal, especially to a child. Therefore, they must keep all patches out of the sight and reach of children, both before and after use.

Opioid-naïve and not opioid-tolerant states

Use of transdermal fentanyl in the opioid-naïve patients has been associated with very rare cases of significant respiratory depression and/or fatality when used as initial opioid therapy, especially in patients with non-cancer-pain. The potential for serious or life-threatening hypoventilation exists even if the lowest dose of transdermal fentanyl is used in initiating therapy in opioid-naïve patients, especially in elderly or patients with hepatic or renal impairment. The tendency of tolerance development varies widely among individuals. It is recommended that Victanyl is used in patients who have demonstrated opioid tolerance (see section 4.2).

Respiratory depression
Some patients may experience significant respiratory depression with Victanyl; patients must be observed for these effects. Respiratory depression may persist beyond the removal of the Victanyl patch. The incidence of respiratory depression increases as the transdermal fentanyl dose is increased (see section 4.9).

Central Nervous System (CNS) depressants, including alcohol and CNS depressant narcotic drugs
Concomitant use of fentanyl with CNS depressants, including alcohol and CNS depressant narcotic drugs, may increase the undesirable effects of fentanyl; concomitant use should be avoided (see section 4.5). If concomitant use of fentanyl with a CNS depressant is clinically necessary, prescribe the lowest effective dosages and minimum duration for both drugs, and follow patients closely for signs of respiratory depression and sedation.

Chronic pulmonary disease
Victanyl may have more severe adverse effects in patients with chronic obstructive or other pulmonary disease. In such patients, opioids may decrease respiratory drive and increase airway resistance.

Drug dependence, tolerance and potential for abuse

For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression).

Additional support and monitoring may be necessary when prescribing for patients at risk of opioid misuse.

A comprehensive patient history should be taken to document concomitant medications, including over-the-counter medicines and medicines obtained on-line, and past and present medical and psychiatric conditions.

Patients may find that treatment is less effective with chronic use and express a need to increase the dose to obtain the same level of pain control as initially experienced. Patients may also supplement their treatment with additional pain relievers. These could be signs that the patient is developing tolerance. The risks of developing tolerance should be explained to the patient.

Overuse or misuse may result in overdose and/or death. It is important that patients only use medicines that are prescribed for them at the dose they have been prescribed and do not give this medicine to anyone else.

Patients should be closely monitored for signs of misuse, abuse, or addiction.
The clinical need for analgesic treatment should be reviewed regularly.

Drug withdrawal syndrome
Prior to starting treatment with any opioids, a discussion should be held with patients to put in place a withdrawal strategy for ending treatment with fentanyl.

Drug withdrawal syndrome may occur upon abrupt cessation of therapy or dose reduction. When a patient no longer requires therapy, it is advisable to taper the dose gradually to minimise symptoms of withdrawal. Tapering from a high dose may take weeks to months.

The opioid drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

If women take this drug during pregnancy, there is a risk that their newborn infants will experience neonatal withdrawal syndrome.

Hyperalgesia
Hyperalgesia may be diagnosed if the patient on long-term opioid therapy presents with increased pain. This might be qualitatively and anatomically distinct from pain related to disease progression or to breakthrough pain resulting from development of opioid tolerance. Pain associated with hyperalgesia tends to be more diffuse than the pre-existing pain and less defined in quality. Symptoms of hyperalgesia may resolve with a reduction of opioid dose.

Central nervous system conditions including increased intracranial pressure
Victanyl should be used with caution in patients who may be particularly susceptible to the intracranial effects of CO_2 retention such as those with evidence of increased

intracranial pressure, impaired consciousness or coma. Victanyl should be used with caution in patients with brain tumours.

Cardiac disease
Fentanyl may produce bradycardia and should therefore be administered with caution to patients with bradyarrhythmias.

Hypotension
Opioids may cause hypotension, especially in patients with acute hypovolaemia. Underlying, symptomatic hypotension and/or hypovolaemia should be corrected before treatment with fentanyl transdermal patches is initiated.

Hepatic impairment
Because fentanyl is metabolised to inactive metabolites in the liver, hepatic impairment might delay its elimination. If patients with hepatic impairment receive Victanyl, they should be observed carefully for signs of fentanyl toxicity and the dose of Victanyl reduced if necessary (see section 5.2).

Renal impairment
Even though impairment of renal function is not expected to affect fentanyl elimination to a clinically relevant extent, caution is advised because fentanyl pharmacokinetics has not been evaluated in this patient population (see section 5.2). If patients with renal impairment receive Victanyl, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary. Additional restrictions apply to opioid-naïve patients with renal impairment (see section 4.2).

Fever/external heat application
Fentanyl concentrations may increase if the skin temperature increases (see section 5.2). Therefore, patients with fever should be monitored for opioid undesirable effects and the Victanyl dose should be adjusted if necessary. There is a potential for temperature-dependent increases in fentanyl released from the system resulting in possible overdose and death.

All patients should be advised to avoid exposing the Victanyl application site to direct external heat sources such as heating pads, electric blankets, heated water beds, heat or tanning lamps, sunbathing, hot water bottles, prolonged hot baths, saunas and hot whirlpool spa baths.

Serotonin Syndrome
Caution is advised when Victanyl is coadministered with medicinal products that affect the serotonergic neurotransmitter systems.

The development of a potentially life-threatening serotonin syndrome may occur with the concomitant use of serotonergic active substances such as Selective Serotonin Re-uptake Inhibitors (SSRIs) and Serotonin Norepinephrine Re-uptake Inhibitors (SNRIs), and with active substances which impair metabolism of serotonin (including Monoamine Oxidase Inhibitors [MAOIs]). This may occur within the recommended dose.

Serotonin syndrome may include mental-status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g, tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g. hyper-reflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g, nausea, vomiting, diarrhoea).

If serotonin syndrome is suspected, treatment with Victanyl should be discontinued.

Interactions with other medicinal products:

CYP3A4 Inhibitors
The concomitant use of Victanyl with cytochrome P450 3A4 (CYP3A4) inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression. Therefore, the concomitant use of Victanyl and CYP3A4 inhibitors is not recommended unless the benefits outweigh the increased risk of adverse effects. Generally, a patient should wait for 2 days after stopping treatment with a CYP3A4 inhibitor before applying the first Victanyl patch. However, the duration of inhibition varies and for some CYP3A4 inhibitors with a long elimination half-life, such as amiodarone or for time-dependent inhibitors such as erythromycin, idelalisib, nicardipine and ritonavir this period may need to be longer. Therefore, the product information of the CYP3A4 inhibitor must be consulted for the active substance's half-life and duration of the inhibitory effect before applying the first Victanyl patch. A patient who is treated with Victanyl should wait at least 1 week after removal of the last patch before initiating treatment with a CYP3A4 inhibitor. If concomitant use of Victanyl with a CYP3A4 inhibitor cannot be avoided, close monitoring for signs or symptoms of increased or prolonged therapeutic effects and adverse effects of fentanyl (in particular respiratory depression) is warranted, and the Victanyl dosage must be reduced or interrupted as deemed necessary (see section 4.5).

Accidental exposure by patch transfer
Accidental transfer of a fentanyl patch to the skin of a non-patch wearer (particularly a child), while sharing a bed or being in close physical contact with a patch wearer, may result in an opioid overdose for the non-patch wearer. Patients should be advised that if accidental patch transfer occurs, the transferred patch must be removed immediately from the skin of the non-patch wearer (see section 4.9).

Use in elderly patients
Data from intravenous studies with fentanyl suggest that elderly patients may have reduced clearance, a prolonged half-life, and they may be more sensitive to the active substance than younger patients. If elderly patients receive Victanyl, they should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see section 5.2).

Gastrointestinal tract
Opioids increase the tone and decrease the propulsive contractions of the smooth muscle of the gastrointestinal tract. The resultant prolongation in gastrointestinal transit time may be responsible for the constipating effect of fentanyl. Patients should be advised on measures to prevent constipation and prophylactic laxative use should be considered. Extra caution should be used in patients with chronic constipation. If paralytic ileus is present or suspected, treatment with Victanyl should be stopped.

Patients with myasthenia gravis
Non-epileptic (myo)clonic reactions can occur. Caution should be exercised when treating patients with myasthenia gravis.

Concomitant use of mixed opioid agonists/antagonists
The concomitant use of buprenorphine, nalbuphine or pentazocine is not recommended (see also section 4.5).

Paediatric population

Victanyl should not be administered to opioid-naïve paediatric patients (see section 4.2). The potential for serious or life-threatening hypoventilation exists regardless of the dose of Victanyl transdermal system administered.
Transdermal fentanyl has not been studied in children under 2 years of age. Victanyl should be administered only to opioid-tolerant children age 2 years or older (see section 4.2).

To guard against accidental ingestion by children, use caution when choosing the application site for Victanyl (see section 4.2 and 6.6) and monitor adhesion of the patch closely.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic related interactions

Centrally-acting medicinal products/Central Nervous System (CNS) depressants, including alcohol and CNS depressant narcotic drugs
The concomitant use of fentanyl with other central nervous system depressants (including benzodiazepines and other sedatives/ hypnotics, opioids, general anaesthetics, phenothiazines, tranquilisers, sedating antihistamines, alcohol and CNS depressant narcotic drugs) and skeletal muscle relaxants may disproportionately increase the CNS depressant effects such as respiratory depression, hypotension, profound sedation, coma or death. Therefore, the use of any of these medicinal products concomitantly with fentanyl requires special patient care and observation.

Monoamine Oxidase Inhibitors (MAOI)
Victanyl is not recommended for use in patients who require the concomitant administration of an MAOI. Severe and unpredictable interactions with MAOIs, involving the potentiation of opiate effects or the potentiation of serotoninergic effects, have been reported. Therefore, Victanyl should not be used within 14 days after discontinuation of treatment with MAOIs.

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

Concomitant use of mixed opioid agonists/antagonists
The concomitant use of buprenorphine, nalbuphine or pentazocine is not recommended. They have high affinity to opioid receptors with relatively low intrinsic activity and therefore partially antagonise the analgesic effect of fentanyl and may induce withdrawal symptoms in opioid dependent patients (see section 4.4).

Pharmacokinetic-related interactions

Cytochrome P450 3A4 (CYP3A4) Inhibitors
Fentanyl, a high clearance active substance, is rapidly and extensively metabolized mainly by CYP3A4.

The concomitant use of transdermal fentanyl with cytochrome P450 3A4 (CYP3A4) inhibitors may result in an increase in fentanyl plasma concentrations, which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression. The extent of interaction with strong CYP3A4 inhibitors is expected to be greater than with weak or moderate CYP3A4 inhibitors. Cases of serious respiratory depression after coadministration of CYP3A4 inhibitors with transdermal fentanyl have been reported, including a fatal case after coadministration with a moderate CYP3A4 inhibitor. The concomitant use of CYP3A4 inhibitors and transdermal fentanyl is not recommended, unless the patient is closely monitored (see section 4.4). Examples of active substances that may increase fentanyl concentrations include: amiodarone, cimetidine, clarithromycin, diltiazem, erythromycin, fluconazole, itraconazole, ketoconazole, nefazodone, ritonavir, verapamil and voriconazole (this list is not exhaustive). After coadministration of weak, moderate or strong CYP3A4 inhibitors with short- term intravenous fentanyl administration, decreases in fentanyl clearance were generally ≤25%, however with ritonavir (a strong CYP3A4 inhibitor), fentanyl clearance decreased on average 67%. The extent of the interactions of CYP3A4 inhibitors with long-term transdermal fentanyl administration is not known, but may be greater than with short-term intravenous administration.

Cytochrome P450 3A4 (CYP3A4) Inducers
The concomitant use of transdermal fentanyl with CYP3A4 inducers may result in a decrease in fentanyl plasma concentrations and a decreased therapeutic effect. Caution is advised upon concomitant use of CYP3A4 inducers and Victanyl. The dose of Victanyl may need to be increased or a switch to another analgesic active substance may be needed. A fentanyl dose decrease and careful monitoring is warranted in anticipation of stopping concomitant treatment with a CYP3A4 inducer. The effects of the inducer decline gradually and may result in increased fentanyl plasma concentrations, which could increase or prolong both the therapeutic and adverse effects, and may cause serious respiratory depression. Careful monitoring should be continued until stable drug effects are achieved. Examples of active substance that may decrease fentanyl plasma concentrations include: carbamazepine, phenobarbital, phenytoin and rifampicin (this list is not exhaustive).

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of transdermal fentanyl in pregnant women. Studies in animals have shown some reproductive toxicity (see section 5.3). The potential risk for humans is unknown, although fentanyl as an IV anaesthetic has been found to cross the placenta in human pregnancies. Victanyl should not be used during pregnancy unless clearly necessary.

Regular use during pregnancy may cause drug dependence in the foetus, leading to withdrawal symptoms in the neonate.

If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Administration during labour may depress respiration in the neonate and an antidote for the child should be readily available.

Breastfeeding
Administration to nursing women is not recommended as fentanyl may be secreted in breast milk and may cause respiratory depression in the infant.

Breastfeeding should therefore be discontinued during treatment with Victanyl and for at least 72 hours after removal of the patch.

Fertility
There are no clinical data on the effects of fentanyl on fertility. Some studies in rats have revealed reduced fertility and enhanced embryo mortality at maternally toxic doses (see section 5.3).

4.7 Effects on ability to drive and use machines

Victanyl may impair mental and/or physical ability required for the performance of potentially hazardous tasks such as driving or operating machinery.

This medicine can impair cognitive function and can affect a patient's ability to drive safely. This class of medicine is in the list of drugs included in regulations under 5a of the Road Traffic Act 1988. When prescribing this medicine, patients should be told:

- The medicine is likely to affect your ability to drive
- Do not drive until you know how the medicine affects you
- It is an offence to drive while under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
    - The medicine has been prescribed to treat a medical or dental problem and
    - You have taken it according to the instructions given by the prescriber and in the information provided with the medicine and
    - It was not affecting your ability to drive safely

4.8 Undesirable effects

The safety of transdermal fentanyl was evaluated in 1565 adult and 289 paediatric subjects who participated in 11 clinical studies (1 double-blind, placebo-controlled; 7 open label, active controlled; 3 open-label uncontrolled) used for the management of chronic malignant or non-malignant pain. These subjects received at least one dose of transdermal fentanyl and provided safety data. Based on pooled safety data from these clinical studies, the most commonly reported (ie ≥10%

incidence) adverse reactions were: nausea (35.7%), vomiting (23.2%), constipation (23.1%), somnolence (15.0%), dizziness (13.1%), and headache (11.8%).

The adverse reactions reported with the use of transdermal fentanyl from these clinical studies, including the above-mentioned adverse reactions, and from post-marketing experiences are listed below in Table 5.

The displayed frequency categories use the following convention:
very common (≥1/10);
common (≥1/100 to <1/10);
uncommon (≥1/1,000 to <1/100);
rare (≥1/10,000 to <1/1,000);
very rare (<1/10,000);
not known (cannot be estimated from the available clinical data).
The adverse reactions are presented by System Organ Class and in order of decreasing seriousness within each frequency category.

System Organ Class	**Table 5: Adverse reactions in adult and paediatric patients**				
	Frequency Category				
	Very Common	Common	Uncommon	Rare	Not Known
Immune System Disorders		Hypersensitivity			Anaphylactic shock, Anaphylactic reaction, Anaphylactoid reaction
Endocrine Disorders					Androgen deficiency
Metabolism and Nutrition Disorders		Anorexia			
Psychiatric Disorders		Insomnia, Depression, Anxiety, Confusional state, Hallucination	Agitation, Disorientation, Euphoric mood,		Delirium. Drug dependence (see section 4.4)

Nervous System Disorders	Somnolence Dizziness, Headache,	Tremor, Paraesthesia,	Hypoaesthesia, Convulsion (including clonic convulsions and grand mal convulsion), Amnesia Depressed level of consciousness, Loss of consciousness		
Eye Disorders			Vision blurred	Miosis	
Ear and Labyrinth Disorders		Vertigo			
Cardiac Disorders		Palpitations, Tachycardia	Bradycardia, Cyanosis		
Vascular Disorders		Hypertension	Hypotension		
Respiratory, Thoracic and Mediastinal Disorders		Dyspnoea	Respiratory depression, Respiratory distress	Apnoea, Hypo-ventilation	Bradypnoea
Gastrointestinal Disorders	Nausea, Vomiting, Constipation	Diarrhoea, Dry mouth, Abdominal pain, Abdominal pain upper, Dyspepsia	Ileus	Subileus	
Skin and Subcutaneous Tissue Disorders		Hyperhidrosis, Pruritus, Rash, Erythema	Eczema, Dermatitis allergic, Skin disorder, Dermatitis, Dermatitis contact		
Musculoskeletal and Connective Tissue Disorders		Muscle spasms	Muscle twitching		
Renal and Urinary Disorders		Urinary retention			
Reproductive System and Breast Disorders			Erectile dysfunction, Sexual dysfunction		
General Disorders and Administration Site Conditions		Fatigue, Oedema peripheral, Asthenia, Malaise Feeling cold	Application site reaction, Influenza like illness, Feeling of body temperature change, Application site hypersensitivity, Drug withdrawal syndrome, Pyrexia*	Application site dermatitis, Application site eczema	

*The assigned frequency (uncommon) is based on analyses of incidence including only adult and paediatric clinical study subjects with non-cancer

pain.

Paediatric population
The safety of transdermal fentanyl was evaluated in 289 paediatric subjects (<18 years) who participated in 3 clinical studies for the management of chronic or continuous pain of malignant or non-malignant origin. These subjects received at least one dose of transdermal fentanyl and provided safety data (see section 5.1).

The safety profile in children and adolescents treated with transdermal fentanyl was similar to that observed in adults. No risk was identified in the paediatric population beyond that expected with the use of opioids for the relief of pain associated with serious illness and there does not appear to be any paediatric-specific risk associated with transdermal fentanyl use in children as young as 2 years old when used as directed.

Based on pooled safety data from these 3 clinical studies in paediatric subjects, the most commonly reported (i.e. ≥10% incidence) adverse reactions were vomiting (33.9%), nausea (23.5%), headache (16.3%), constipation (13.5%), diarrhoea (12.8%), and pruritus (12.8%).

Tolerance, physical dependence, and psychological dependence can develop on repeated use of transdermal fentanyl (see section 4.4).

Opioid withdrawal symptoms (such as nausea, vomiting, diarrhoea, anxiety, and shivering) are possible in some patients after conversion from their previous opioid analgesic to Victanyl or if therapy is stopped suddenly (see section 4.2).

There have been very rare reports of newborn infants experiencing neonatal withdrawal syndrome when mothers chronically used transdermal fentanyl during pregnancy (see section 4.6).

Cases of serotonin syndrome have been reported when fentanyl was administered concomitantly with highly serotonergic drugs (see sections 4.4. and 4.5).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Patients should be informed of the signs and symptoms of overdose and to ensure that family and friends are also aware of these signs and to seek immediate medical help if they occur.

Symptoms and signs
The manifestations of fentanyl overdose are an extension of its pharmacologic actions, the most serious effects being respiratory depression.

Treatment

For management of respiratory depression immediate countermeasures, include removing the fentanyl patch and physically or verbally stimulating the patient. These actions can be followed by administration of a specific opioid antagonist such as naloxone.

Respiratory depression following an overdose may outlast the duration of action of the opioid antagonist. The interval between IV antagonist doses should be carefully chosen because of the possibility of re-narcotization after the patch is removed; repeated administration or a continuous infusion of naloxone may be necessary. Reversal of the narcotic effect may result in acute onset of pain and release of catecholamines.

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

If severe or persistent hypotension occurs, hypovolemia should be considered, and the condition should be managed with appropriate parenteral fluid therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, Opioids; Phenylpiperidine derivatives, ATC code: N02AB03

Mechanism of action
Fentanyl is an opioid analgesic, interacting predominantly with the μ opioid receptor. Its primary therapeutic actions are analgesia and sedation.

Paediatric population
The safety of fentanyl transdermal patch was evaluated in 3 open-label studies in 289 paediatric subjects with chronic pain, aged 2 to 17 years, inclusive. Eighty of the children were aged 2 to 6 years, inclusive. Of the 289 subjects enrolled in these 3 studies, 110 initiated transdermal fentanyl treatment with a dosage of 12 mcg/h. Of these 110 subjects, 23 (20.9%) had previously been receiving <30 mg of oral morphine equivalents per day, 66 (60.0%) had been receiving 30 to 44 mg of oral morphine equivalents per day, and 12 (10.9%) had been receiving at least 45 mg of oral morphine equivalents per day (data not available for 9 [8.2%] subjects). Starting dosages of 25 mcg/h and higher were used by the remaining 179 subjects, 174 (97.2%) of whom had been on opioid doses of at least 45 mg of oral morphine equivalents per day. Among the remaining 5 subjects with a starting dosage of at least 25 mcg/h whose prior opioid doses were <45 mg of oral morphine equivalents per day, 1 (0.6%) had previously been receiving <30 mg of oral morphine equivalents per day and 4 (2.2%) had been receiving 30 to 44 mg of oral morphine equivalents per day (see section 4.8).

5.2 Pharmacokinetic properties

Absorption

Transdermal fentanyl provides continuous systemic delivery of fentanyl during the 72-hour application period. Following transdermal fentanyl application, the skin under the system absorbs fentanyl, and a depot of fentanyl concentrates in the upper skin layers. Fentanyl then becomes available to the systemic circulation. The polymer matrix and the diffusion of fentanyl through the layers of the skin ensure that the release rate is relatively constant.The concentration gradient existing between the system and the lower concentration in the skin drives drug release. The average bioavailability of fentanyl after application of the transdermal patch is 92%.

After the first transdermal fentanyl application, serum fentanyl concentrations increase gradually, generally leveling off between 12 and 24 hours, and remaining relatively constant for the remainder of the 72-hour application period. By the end of the second 72-hour application, a steady state serum concentration is reached and is maintained during subsequent applications of a patch of the same size. Due to accumulation, the AUC and Cmax values over a dosing interval at steady state are approximately 40% higher than after a single application. Patients reach and maintain a steady-state serum concentration that is determined by individual variation in skin permeability and body clearance of fentanyl. High inter-subject variability in plasma concentrations has been observed.

A pharmacokinetic model has suggested that serum fentanyl concentrations may increase by 14% (range 0-26%) if a new patch is applied after 24 hours rather than the recommended 72-hour application.

Skin temperature elevation may enhance the absorption of transdermally-applied fentanyl (see section 4.4). An increase in skin temperature through the application of a heating pad on low setting over the transdermal fentanyl system during the first 10 hours of a single application increased the mean fentanyl AUC value by 2.2-fold and the mean concentration at the end of heat application by 61%.

Distribution

Fentanyl is rapidly distributed to various tissues and organs, as indicated by the large volume of distribution (3 to 10 L/kg after intravenous dosing in patients). Fentanyl accumulates in skeletal muscle and fat and is released slowly into blood.

In a study in cancer patients treated with transdermal fentanyl, plasma protein binding was on average 95% (range 77-100%). Fentanyl crosses the blood-brain barrier easily. It also crosses the placenta and is excreted in breast milk.

Biotransformation

Fentanyl is a high clearance active substance and is rapidly and extensively metabolised primarily by CYP3A4 in the liver. The major metabolite, norfentanyl, and other metabolites are inactive. Skin does not appear to metabolise fentanyl delivered transdermally. This was determined in a human keratinocyte cell assay and in clinical studies in which 92% of the dose delivered from the system was accounted for as unchanged fentanyl that appeared in the systemic circulation.

Elimination

Following a 72-hour patch application, the mean fentanyl half-life ranges from 20 to 27 hours As a result of continued absorption of fentanyl from the skin depot after removal of the patch, the half-life of fentanyl after transdermal administration is about 2- to 3-fold longer than intravenous administration.

After intravenous administration, fentanyl mean total clearance values across studies range in general between 34 and 66 L/h.

Within 72 hours of IV fentanyl administration, approximately 75% of the dose is excreted into the urine and approximately 9% of the dose into the faeces. Excretion occurs primarily, as metabolites, with less than 10% of the dose excreted as unchanged active substance

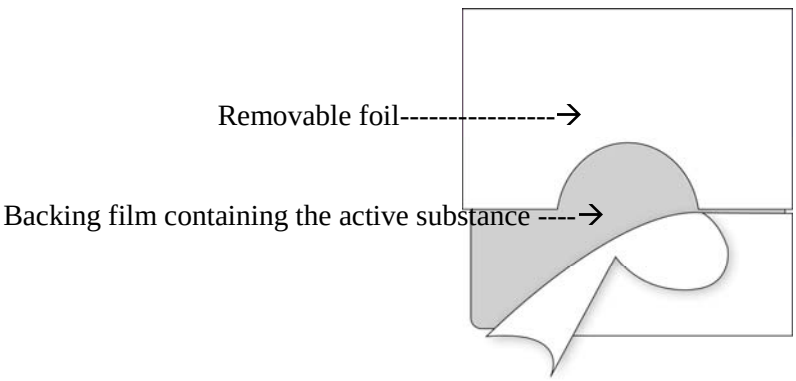
Linearity/non-Linearity

The serum fentanyl concentrations attained are proportional to the transdermal fentanyl patch size. The pharmacokinetics of transdermal fentanyl do not change with repeated application.

Pharmacokinetic/Pharmacodynamic Relationships

There is a high inter-subject variability in fentanyl pharmacokinetics, in the relationships between fentanyl concentrations, therapeutic and adverse effects, and in opioid tolerance. The minimum effective fentanyl concentration depends on the pain intensity and the previous use of opioid therapy. Both the minimum effective concentration and the toxic concentration increase with tolerance. An optimal therapeutic concentration range of fentanyl can therefore not be established. Adjustment of the individual fentanyl dose must be based on the patient's response and level of tolerance. A lag time of 12 to 24 hours after application of the first patch and after a dose increase must be taken into account.

The transdermal patch is an application form for the systemic administration of fentanyl, which ensures that an adequate serum level of fentanyl will be maintained over a period of 72 hours with a constant rate of release.



Removable foil----------→

The transdermal patch consists of two functional layers:

The topside consists of a waterproof backing film with a self-adhesive fentanyl-containing matrix layer on it. This matrix layer is covered by a removable foil which – due to slits - can be easily removed prior to use.

The 4.25 cm^2 patch delivers approximately 12 micrograms/hour fentanyl to the skin. This is achieved by means of the polymer matrix: A concentration gradient is created between the polymer matrix with high concentrations of the active substance fentanyl and the skin with low concentration of fentanyl. Over a period of 72 hours fentanyl diffuses towards the lower concentration, i.e. towards the skin.

The relative bioavailability of fentanyl from the patch is 92%. The serum fentanyl concentrations attained are proportional to the patch size.

Special populations

Elderly

Data from intravenous studies with fentanyl suggest that elderly patients may have reduced clearance, a prolonged half-life, and they may be more sensitive to the drug than younger patients. In a study conducted with transdermal fentanyl, healthy elderly subjects had fentanyl pharmacokinetics which did not differ significantly from healthy young subjects although peak serum concentrations tended to be lower and mean half-life values were prolonged to approximately 34 hours. Elderly patients should be observed carefully for signs of fentanyl toxicity and the dose reduced if necessary (see section 4.4).

Renal impairment

The influence of renal impairment on the pharmacokinetics of fentanyl is expected to be limited because urinary excretion of unchanged fentanyl is less than 10% and there are no known active metabolites eliminated by the kidney. However, as the influence of renal impairment on the pharmacokinetics of fentanyl has not been evaluated, caution is advised (see sections 4.2 and 4.4).

Hepatic impairment

Patients with hepatic impairment should be observed carefully for signs of fentanyl toxicity and the dose of transdermal fentanyl should be reduced if necessary (see section 4.4). Data in subjects with cirrhosis and simulated data in subjects with different grades of impaired liver function treated with transdermal fentanyl suggest that fentanyl concentrations may be increased, and fentanyl clearance may be decreased compared to subjects with normal liver function. The simulations suggest that the steady-state AUC of patients with Child-Pugh Grade B liver disease (Child-Pugh Score =8) would be approximately 1.36 times larger compared with that of patients with normal liver function (Grade A; Child-Pugh Score =5.5). As for patients with Grade C liver disease (Child-Pugh Score =12.5), the results indicate that fentanyl concentration accumulates with each administration, leading these patients to have an approximately 3.72 times larger AUC at steady state.

Paediatric Population

Fentanyl concentrations were measured in more than 250 children aged 2 to 17 years who were applied fentanyl patches in the dose range of 12.5 to 300 mcg/h. Adjusting for body weight, clearance (L/h/kg) appears to be approximately 80% higher in children 2 to 5 years old and 25% higher in children 6 to 10 years old when compared to children 11 to 16 years old, who are expected to have a similar clearance as adults. These findings have been taken into consideration in determining the dosing recommendations for paediatric patients (see sections 4.2 and 4.4).

5.3 Preclinical safety data

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

Standard reproductive and developmental toxicity studies have been carried out using parenteral administration of fentanyl. In a rat study fentanyl did not influence male fertility. Some studies with female rats revealed reduced fertility and enhanced embryo mortality.

Effects on the embryo were due to maternal toxicity and not to direct effects of the substance on the developing embryo. There was no indication of teratogenic effects in studies in two species (rats and rabbits). In a study on pre- and postnatal development the survival rate of offspring was significantly reduced at doses which slightly reduced maternal weight. This effect could either be due to altered maternal care or a direct effect of fentanyl on the pups. Effects on somatic development and behaviour of the offspring were not observed.

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

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Matrix Components:

Aloe vera leaf extract oil (on the basis of soya oil tocopherol acetate)

Pentaerythriol esters of hydrogenated colophony
Poly(2-ethylhexylacrylate,vinylacetate) (50:50)

Release liner:
Polyethylene terephtalat, polyester, siliconized

Backing foil with imprint:
Polyethylene terephthalat foil,
Blue printing colour

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

Only open the pouch immediately before use of the patch.

6.5 Nature and contents of container

Each transdermal patch is packed individually into a sealed child resistant pouch. The pouch is composed of Polyflex foil (a laminate foil made up of, PET, aluminium foil and a Surlyn heat-sealable layer) and is tightly sealed.

5, 10, 16, 20 transdermal patches

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Please refer to section 4.2 for instructions on how to apply the patch. There are no safety and pharmacokinetic data available for other application sites.

High quantities of fentanyl remain in the transdermal patches even after use. Used patches should be folded so that the adhesive side of the patch adheres to itself and then they should be safely discarded out of the reach of children. Unused patches should be returned to the (hospital) pharmacy.

Wash hands with water only after applying or removing the patch.

7 MARKETING AUTHORISATION HOLDER

Accord-UK Ltd

(Trading style: Accord)

Whiddon Valley

Barnstaple

Devon

EX32 8NS

8 MARKETING AUTHORISATION NUMBER(S)

PL 00142/1040

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/10/2019

10 DATE OF REVISION OF THE TEXT

03/06/2020