SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Butec 20 microgram/hour Transdermal Patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each transdermal patch contains 20 mg of buprenorphine in a 25 cm^2 area releasing a nominal 20 micrograms of buprenorphine per hour over a period of 7 days.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch.

Beige coloured patch with rounded corners.

Square patch marked: ***Butec*** 20 μg/h

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of non-malignant pain of moderate intensity when an opioid is necessary for obtaining adequate analgesia

Butec is not suitable for the treatment of acute pain.

Butec is indicated in adults.

4.2 Posology and method of administration

Posology

Butec should be administered once per week on the same day each week.

Patients aged 18 years and over:
The lowest ***Butec*** dose (***Butec*** 5 microgram/hour transdermal patch) should be used as the initial dose. Consideration should be given to the previous opioid history of the patient (see section 4.5) as well as to the current general condition and medical status of the patient.

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

Titration:
During initiation of treatment with ***Butec***, short-acting supplemental analgesics may be required as needed until analgesic efficacy with ***Butec*** is attained.

The dose of ***Butec*** may be titrated upwards as indicated after 3 days, when the maximum effect of a given dose is established. Subsequent dosage increases may then be titrated based on the need for supplemental pain relief and the patient's analgesic response to the patch.

To increase the dose, a larger patch should replace the patch that is currently being worn, or a combination of patches should be applied in different places to achieve the desired dose. It is recommended that no more than two patches are applied at the same time, up to a maximum total dose of 40 microgram/hour. A new patch should not be applied to the same skin site for the subsequent 3-4 weeks (see section 5.2). Patients should be carefully and regularly monitored to assess the optimum dose and duration of treatment.

Conversion from opioids:
Butec can be used as an alternative to treatment with other opioids. Such patients should be started on the lowest available dose (***Butec*** 5 microgram/hour transdermal patch) and continue taking short-acting supplemental analgesics during titration, as required.

Paediatric population:
The safety and efficacy of ***Butec*** in children below 18 years of age has not been established. No data are available.

Elderly:
No dosage adjustment of ***Butec*** is required in elderly patients.

Renal impairment:
No special dose adjustment of ***Butec*** is necessary in patients with renal impairment.

Hepatic impairment:
Buprenorphine is metabolised in the liver. The intensity and duration of its action may be affected in patients with impaired liver function. Therefore patients with hepatic insufficiency should be carefully monitored during treatment with ***Butec***.

Patients with severe hepatic impairment may accumulate buprenorphine during ***Butec*** treatment. Consideration of alternate therapy should be considered, and ***Butec*** should be used with caution, if at all, in such patients.

Method of administration

Route of administration:
Transdermal patch to be worn for 7 days. The patch must not be divided or cut into pieces.

Patch application:
In order to ensure effective analgesia of buprenorphine and to minimise the potential for skin reactions (see section 4.4.) the following directions of use should be followed.

Butec should be applied to non-irritated, intact skin of the upper outer arm, upper chest, upper back or the side of the chest, but not to any parts of the skin with large scars. ***Butec*** should be applied to a relatively hairless or nearly hairless skin site. If none are available, the hair at the site should be cut with scissors, not shaven.

If the application site must be cleaned, it should be done with clean water only. Soaps, alcohol, oils, lotions or abrasive devices must not be used. The skin must be dry before the patch is applied. ***Butec*** should be applied immediately after removal from the sealed sachet. Following removal of the protective layer, the transdermal patch should be pressed firmly in place with the palm of the hand for approximately 30 seconds, making sure the contact is complete, especially around the edges. If the edges of the patch begin to peel off, the edges may be taped down with suitable skin tape to ensure a 7 day period of wear. The patch should be worn continuously for 7 days. Bathing, showering, or swimming should not affect the patch. If a patch falls off, a new one should be applied and worn for 7 days.

Duration of administration:
Butec should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with ***Butec*** is necessary in view of the nature and severity of the illness, then careful and regular monitoring should be carried out (if necessary with breaks in treatment) to establish whether and to what extent further treatment is necessary.

Treatment goals and Discontinuation:

Before initiating treatment with ***Butec***, a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with ***Butec***, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

After removal of the patch, buprenorphine serum concentrations decrease gradually and thus the analgesic effect is maintained for a certain amount of time. This should be considered when therapy with ***Butec*** is to be followed by other opioids. As a general rule, a subsequent opioid should not be administered within 24 hours after

removal of the patch. At present, only limited information is available on the starting dose of other opioids administered after discontinuation of the transdermal patch (see section 4.5).

Patients with fever or exposed to external heat:
While wearing the patch, patients should be advised to avoid exposing the application site to external heat sources, such as heating pads, electric blankets, hot water bottles, heat lamps, sauna, hot tubs, and heated water beds, etc., as an increase in absorption of buprenorphine may occur.

When treating febrile patients, one should be aware that fever may also increase absorption resulting in increased plasma concentrations of buprenorphine and thereby increased risk of opioid reactions.

Duration of treatment

Butec should not be used longer than necessary.

4.3 Contraindications

Butec is contra-indicated in:
- patients with known hypersensitivity to the active substance buprenorphine or to any of the excipients, including previous history of application site reactions suggestive of allergic contact dermatitis with buprenorphine transdermal patches (see section 6.1)
- opioid dependent patients and for narcotic withdrawal treatment
- conditions in which the respiratory centre and function are severely impaired or may become so
- patients who are receiving MAO inhibitors or have taken them within the last two weeks (see section 4.5)
- patients suffering from myasthenia gravis
- patients suffering from delirium tremens.

4.4 Special warnings and precautions for use

Butec should be used with particular caution in patients with severely impaired respiratory function, sleep apnoea, acute alcohol intoxication, head injury, shock, a reduced level of consciousness of uncertain origin, intracranial lesions or increased intracranial pressure, severe hepatic impairment (see section 4.2) or constipation.

The primary risk of opioid excess is respiratory depression.

Sleep-related breathing disorders
Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the total opioid dosage.

Concomitant use of ***Butec*** and sedative medicines such as benzodiazepines or related drugs may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicines should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe ***Butec*** concomitantly with sedative medicines, the lowest effective dose should be used, and the duration of treatment should be as short as possible.

The patients should be followed closely for signs and symptoms of respiratory depression and sedation. In this respect, it is strongly recommended to inform patients and their caregivers to be aware of these symptoms (see section 4.5).

Significant respiratory depression has been associated with buprenorphine, particularly by the intravenous route. A number of overdose deaths have occurred when addicts have intravenously abused buprenorphine, usually with benzodiazepines concomitantly. Additional overdose deaths due to ethanol and benzodiazepines in combination with buprenorphine have been reported.

Serotonin syndrome

Concomitant administration of ***Butec*** and other serotonergic agents, such as selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).

If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

Skin reactions at application site

Application site reactions usually present as a mild to moderate skin inflammation (contact dermatitis) with erythema, oedema, pruritis, rash, vesicles and pain or a burning sensation at the application site. The reaction typically resolves spontaneously following removal of the ***Butec*** patch. Adherence to the method of administration given in section 4.2 reduces the risk of skin reactions at the application site.

Butec patches may also cause skin sensitisation and subsequent immune-mediated, type IV hypersensitivity reaction allergic contact dermatitis. Allergic contact dermatitis may develop with a significant delay of up to several months following initiation of treatment with ***Butec*** patches. This may manifest either with symptoms similar to irritant contact dermatitis or with more severe symptoms, including burn-like lesions with bullae and discharge which spread beyond the application site and may not resolve rapidly

following removal of the patch. Patients and caregivers should be instructed to monitor the application site for such reactions.

If allergic contact dermatitis is suspected, relevant diagnostic procedures should be performed to determine whether sensitisation has occurred and is caused by the patches. If allergic contact dermatitis is confirmed treatment should be discontinued (see section 4.3). Continued treatment with ***Butec*** patches in patients experiencing allergic contact dermatitis may lead to complications, including blistering of the skin, open wound, bleeding, ulceration and subsequent infections. Mechanical injuries during patch removal, such as laceration, are also possible in patients with fragile skin. Chronic inflammation may lead to long-lasting sequelae such as post-inflammatory hyper- and hypopigmentation, as well as dry and thick scaly lesions which may closely resemble scars.

Buprenorphine may lower the seizure threshold in patients with a history of seizure disorder.

Since CYP3A4 inhibitors may increase concentrations of buprenorphine (see section 4.5), patients already treated with CYP3A4 inhibitors should have their dose of ***Butec*** carefully titrated since a reduced dosage might be sufficient in these patients.

Butec is not recommended for analgesia in the immediate post-operative period or in other situations characterised by a narrow therapeutic index or a rapidly varying analgesic requirement. Prolonged release opioids should not be used for acute post-operative pain owing to the increased risk of persistent post-operative opioid use (PPOU) and opioid-induced ventilatory impairment (OIVI).

<u>Tolerance and opioid use disorder (abuse and dependence)</u>
Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as ***Butec***. Repeated use of ***Butec*** can lead to OUD. A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of ***Butec*** may result in overdose and/or death. The risk of developing OUD is increased in patients with a personal or a family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users or in patients with a personal history of other mental health disorders (e.g. major depression, anxiety and personality disorders).

Before initiating treatment with ***Butec*** and during the treatment, treatment goals and a discontinuation plan should be agreed with the patient (see section 4.2). Before and during treatment the patient should also be informed about the risks and signs of OUD. If these signs occur, patients should be advised to contact their physician.

Patients will require monitoring for signs of drug-seeking behavior (e.g. too early requests for refills). This includes the review of concomitant opioids and

psycho-active drugs (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered.

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 buprenorphine.

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.

Withdrawal syndrome, when it occurs, is generally mild, begins after 2 days and may last up to 2 weeks. 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.

Butec should not be used at higher doses than recommended.

4.5 Interaction with other medicinal products and other forms of interaction

Butec must not be used concomitantly with MAOIs or in patients who have received MAOIs within the previous two weeks (see section 4.3).

Butec should be used cautiously when co-administered with serotonergic medicinal products, such as selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

Effect of other active substances on the pharmacokinetics of buprenorphine:

Buprenorphine is primarily metabolised by glucuronidation and to a lesser extent (about 30%) by CYP3A4. Concomitant treatment with CYP3A4 inhibitors may lead to elevated plasma concentrations with intensified efficacy of buprenorphine. Studies with the CYP3A4 inhibitor ketoconazole did not produce clinically relevant increases in mean maximum (C_{max}) or total (AUC) buprenorphine exposure following ***Butec*** with ketoconazole as compared to ***Butec*** alone.

The interaction between buprenorphine and CYP3A4 enzyme inducers has not been studied. Co-administration of ***Butec*** and enzyme inducers (e.g. phenobarbital, carbamazepine, phenytoin and rifampicin) could lead to increased clearance which might result in reduced efficacy.

Reductions in hepatic blood flow induced by some general anaesthetics (e.g. halothane) and other medicinal products may result in a decreased rate of hepatic elimination of buprenorphine.

Pharmacodynamic interactions:
Butec should be used cautiously with other central nervous system depressants such as other opioid derivatives (analgesics and antitussives containing e.g. morphine, codeine or dextromethorphan), certain antidepressants, sedative H1-receptor antagonists, alcohol, anxiolytics, neuroleptics, clonidine and related substances. These combinations increase the CNS depressant activity.

The concomitant use of ***Butec*** with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death (see section 4.4).

Concomitant administration of buprenorphine with anticholinergics or medications with anticholinergic activity (e.g. tricyclic antidepressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may results in increased anticholinergic adverse effects.

The concomitant use of opioids with sedative medicines such as benzodiazepines or related drugs increases the risk of sedation, respiratory depression, coma and death because of additive CNS depressant effect. The dose and duration of concomitant use should be limited (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of ***Butec*** in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Therefore ***Butec*** should not be used during pregnancy and in women of childbearing potential who are not using effective contraception.

Towards the end of pregnancy high doses of buprenorphine may induce respiratory depression in the neonate even after a short period of administration.

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 buprenorphine is secreted in breast milk and may cause respiratory depression in the infant. Studies in rats have shown that buprenorphine may inhibit lactation. Available pharmacodynamic/ toxicological data in animals has shown excretion of buprenorphine into the milk (see section 5.3). Therefore the use of ***Butec*** during lactation should be avoided.

Fertility
No human data on the effect of buprenorphine on fertility are available. In a fertility and early embryonic development study, no effects on reproductive parameters were observed in male or female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

Butec has a major influence on the ability to drive and use machines. Even when used according to instructions, ***Butec*** may affect the patient's reactions to such an extent that road safety and the ability to operate machinery may be impaired. This applies particularly in the beginning of treatment and in conjunction with other centrally acting substances including alcohol, tranquillisers, sedatives and hypnotics. An individual recommendation should be given by the physician. A general restriction is not necessary in cases where a stable dose is used.

Patients who are affected and experience side effects (e.g. dizziness, drowsiness, blurred vision) during treatment initiation or titration to a higher dose should not drive or use machines, nor for at least 24 hours after the patch has been removed.

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 you have this medicine in your body over a specified limit unless you have a defence (called the 'statutory defence'). This defence applies when:
- 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.

- Please note that it is still an offence to drive if you are unfit because of the medicine (i.e. your ability to drive is being affected).

Details regarding a new driving offence concerning driving after drugs have been taken in the UK may be found here: https://www.gov.uk/drug-driving-law

4.8 Undesirable effects

Serious adverse reactions that may be associated with ***Butec*** therapy in clinical use are similar to those observed with other opioid analgesics, including respiratory depression (especially when used with other CNS depressants) (see section 4.4).

The following frequency categories form the basis for classification of the undesirable effects:

Term	Frequency
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
Frequency not known	Cannot be estimated from the available data

Immune system disorders:
Uncommon: hypersensitivity.
Rare: anaphylactic reaction.
Frequency not known: anaphylactoid reaction.

Metabolism and nutrition disorders:
Common: anorexia.
Rare: dehydration.

Psychiatric disorders:
Common: confusion, depression, insomnia, nervousness, anxiety.
Uncommon: affect lability, sleep disorder, restlessness, agitation, euphoric mood, hallucinations, decreased libido, nightmares, aggression.
Rare: psychotic disorder.
Very rare: mood swings.
Frequency not known: drug dependence (see section 4.4), depersonalisation.

Nervous system disorders:
Very common: headache, dizziness, somnolence.
Common: tremor.

Uncommon: sedation, dysgeusia, dysarthria, hypoaesthesia, memory impairment, migraine, syncope, abnormal co-ordination, disturbance in attention, paraesthesia.
Rare: balance disorder, speech disorder.
Very rare: involuntary muscle contractions.
Frequency not known: seizure, hyperalgesia, sleep apnoea syndrome.

Eye disorders:
Uncommon: dry eye, blurred vision.
Rare: visual disturbance, eyelid oedema, miosis.

Ear and labyrinth disorders:
Uncommon: tinnitus, vertigo.
Very rare: ear pain.

Cardiac disorders:
Uncommon: palpitations, tachycardia
Rare: angina pectoris.

Vascular disorders:
Uncommon: hypotension, circulatory collapse, hypertension, flushing.
Rare: vasodilation, orthostatic hypotension.

Respiratory, thoracic and mediastinal disorders:
Common: dyspnoea.
Uncommon: cough, wheezing, hiccups.
Rare: respiratory depression, respiratory failure, asthma aggravated, hyperventilation, rhinitis.

Gastrointestinal disorders:
Very common: constipation, nausea, vomiting.
Common: abdominal pain, diarrhoea, dyspepsia, dry mouth.
Uncommon: flatulence.
Rare: dysphagia, ileus.
Frequency not known: diverticulitis.

Hepatobiliary disorders:
Frequency not known: biliary colic.

Skin and subcutaneous tissue disorders:
Very common: pruritis, erythema.
Common: rash, sweating, exanthema.
Uncommon: dry skin, urticaria.
Rare: face oedema.
Very rare: pustules, vesicles.
Frequency not known: Dermatitis contact, skin discolouration.

Musculoskeletal and connective tissue disorders:
Common: muscular weakness.
Uncommon: myalgia, muscle spasms.

Renal and urinary disorders:
Uncommon: urinary incontinence, urinary retention, urinary hesitation.

Reproductive system and breast disorders:
Rare: erectile dysfunction, sexual dysfunction.

General disorders and administration site conditions:
Very common: application site skin reactions*.
Common: tiredness, asthenic conditions, peripheral oedema.
Uncommon: fatigue, pyrexia, rigors, oedema, drug withdrawal syndrome, chest pain.
Rare: influenza-like illness.
Frequency not known: neonatal drug withdrawal syndrome, drug tolerance.

* Includes common signs and symptoms of contact dermatitis (irritative or allergic): erythema, oedema, pruritis, rash, vesicles and pain/burning sensation at the application site. In some cases late onset allergic contact dermatitis has occurred with marked signs of inflammation. In such cases treatment with ***Butec*** patches should be terminated.

Investigations:
Uncommon: alanine aminotransferase increased, weight decreased.

Injury, poisoning and procedural complications:
Uncommon: accidental injury, fall

Drug dependence
Repeated use of ***Butec*** can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

After discontinuation of ***Butec***, withdrawal symptoms are uncommon. This may be due to the very slow dissociation of buprenorphine from the opioid receptors and to the gradual decrease of buprenorphine plasma concentrations (usually over a period of 30 hours after removal of the last patch).

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 the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms: Symptoms similar to those of other centrally acting analgesics are to be expected. These include respiratory depression, sedation, drowsiness, nausea, vomiting, cardiovascular collapse and marked miosis.

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.

Treatment: Remove any patches from the patient's skin. Establish and maintain a patent airway, assist or control respiration as indicated and maintain adequate body temperature and fluid balance. Oxygen, intravenous fluids, vasopressors and other supportive measures should be employed as indicated.

A specific opioid antagonist such as naloxone may reverse the effects of buprenorphine, although naloxone may be less effective in reversing the effects of buprenorphine than other mu-opioid agonists. Treatment with continuous intravenous naloxone should begin with the usual doses but high doses may be required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, opioids; ATC code: N02 AE01

Buprenorphine is an agonist opioid, acting at the mu opioid receptor. It also has antagonistic activity at the kappa opioid receptor.

Efficacy has been demonstrated in seven pivotal phase III studies of up to 12 weeks duration in patients with non-malignant pain of various aetiologies. These included patients with moderate and severe OA and back pain. ***Butec*** demonstrated clinically significant reductions in pain scores (approximately 3 points on the BS-11 scale) and significantly greater pain control compared with placebo.

A long term, open-label extension study (n=384) has also been performed in patients with non-malignant pain. With chronic dosing, 63% of patients were maintained in pain control for 6 months, 39% of patients for 12 months, 13% of patients for 18 months and 6% for 21 months. Approximately 17% were stabilised on the 5 mg dose, 35% on the 10 mg dose and 48% on the 20 mg dose.

5.2 Pharmacokinetic properties

There is evidence of enterohepatic recirculation.

Studies in non-pregnant and pregnant rats have shown that buprenorphine passes the blood-brain and placental barriers. Concentrations in the brain (which contained only unchanged buprenorphine) after parenteral

administration were 2-3 times higher than after oral administration. After intramuscular or oral administration buprenorphine apparently accumulates in the foetal gastrointestinal lumen – presumably due to biliary excretion, as enterohepatic circulation has not fully developed.

Each patch provides a steady delivery of buprenorphine for up to seven days. Steady state is achieved during the first application. After removal of ***Butec***, buprenorphine concentrations initially decline at a rate of approximately 50% in 12 hours. Thereafter, mean elimination half-lives have been reported to be between 30 and 45 hours.

Absorption:
Following ***Butec*** application, buprenorphine diffuses from the patch through the skin. In clinical pharmacology studies, the median time for "***Butec*** 10 microgram/hour" to deliver detectable buprenorphine concentrations (25 picograms/ml) was approximately 17 hours. Analysis of residual buprenorphine in patches after 7-day use shows 15% of the original load delivered. A study of bioavailability, relative to intravenous administration, confirms that this amount is systemically absorbed. Buprenorphine concentrations remain relatively constant during the 7-day patch application.

Application site:
A study in healthy subjects demonstrated that the pharmacokinetic profile of buprenorphine delivered by ***Butec*** is similar when applied to upper outer arm, upper chest, upper back or the side of the chest (midaxillary line, 5th intercostal space). The absorption varies to some extent depending on the application site and the exposure is at the most approximately 26 % higher when applied to the upper back compared to the side of the chest.

In a study of healthy subjects receiving ***Butec*** repeatedly to the same site, an almost doubled exposure was seen with a 14 day rest period. For this reason, rotation of application sites is recommended, and a new patch should not be applied to the same skin site for 3-4 weeks.

In a study of healthy subjects, application of a heating pad directly on the transdermal patch caused a transient 26 - 55% increase in blood concentrations of buprenorphine. Concentrations returned to normal within 5 hours after the heat was removed. For this reason, applying direct heat sources such as hot water bottles, heat pads or electric blankets directly to the patch is not recommended. A heating pad applied to a ***Butec*** site immediately after patch removal did not alter absorption from the skin depot.

Distribution:
Buprenorphine is approximately 96% bound to plasma proteins.

Studies of intravenous buprenorphine have shown a large volume of distribution, implying extensive distribution of buprenorphine. In a study of intravenous buprenorphine in healthy subjects, the volume of distribution at steady state was 430l, reflecting the large volume of distribution and lipophilicity of the active substance.

Following intravenous administration, buprenorphine and its metabolites are secreted into bile, and within several minutes, distributed into the cerebrospinal fluid. Buprenorphine concentrations in the cerebrospinal fluid appear to be approximately 15% to 25% of concurrent plasma concentrations.

Biotransformation and elimination:
Buprenorphine metabolism in the skin following ***Butec*** application is negligible. Following transdermal application, buprenorphine is eliminated via hepatic metabolism, with subsequent biliary excretion and renal excretion of soluble metabolites. Hepatic metabolism, through CYP3A4 and UGT1A1/1A3 enzymes, results in two primary metabolites, norbuprenorphine and buprenorphine 3-O-glucuronide, respectively. Norbuprenorphine is glucuronidated before elimination. Buprenorphine is also eliminated in the faeces. In a study in post-operative patients, the total elimination of buprenorphine was shown to be approximately 55l/h.

Norbuprenorphine is the only known active metabolite of buprenorphine.

Effect of buprenorphine on the pharmacokinetics of other active substances:
Based on *in vitro* studies in human microsomes and hepatocytes, buprenorphine does not have the potential to inhibit metabolism catalysed by the CYP450 enzymes CYP1A2, CYP2A6 and CYP3A4 at concentrations obtained with use of ***Butec*** 20 microgram/hour transdermal patch. The effect on metabolism catalysed by CYP2C8, CYP2C9 and CYP2C19 has not been studied.

5.3 Preclinical safety data

Reproductive and developmental toxicity

No effect on fertility or general reproductive performance was observed in rats treated with buprenorphine. In embryofoetal developmental toxicity studies conducted in rats and rabbits using buprenorphine, no embryofoetal toxicity effects were observed. In a rat pre- and post-natal developmental toxicity study with buprenorphine there was pup mortality, decreased pup body weight and concomitant maternal reduced food consumption and clinical signs.

Genotoxicity

A standard battery of genotoxicity tests indicated that buprenorphine is non-genotoxic.

Carcinogenicity

In long-term studies in rats and mice there was no evidence of any carcinogenic potential relevant for humans.

Systemic toxicity and dermal toxicity

In single- and repeat dose toxicity studies in rats, rabbits, guinea pigs, dogs and minipigs, ***Butec*** caused minimal or no adverse systemic events, whereas skin irritation was observed in all species examined.

Toxicological data available did not indicate a sensitising potential of the additives of the transdermal patches.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Adhesive matrix (containing buprenorphine):

[(Z)-octadec-9-en-1-yl] (Oleyl oleate),

Povidone K90,

4-oxopentanic acid, (Levulinic Acid)

Poly[acrylic acid-co-butylacrylate-co-(2-ethylhexyl)acrylate-co-vinylacetate] (5:15:75:5), cross-linked (DuroTak 387-2054)

Adhesive matrix (without buprenorphine):

Poly[acrylic acid-co-butylacrylate-co-(2-ethylhexyl) acrylate-co-vinylacetate] (5:15:75:5), not cross-linked (DuroTak 387-2051).

Separating foil between the adhesive matrices with and without buprenorphine: Poly(Ethyleneterephthalate) – foil.

Backing layer:

Poly(Ethyleneterephthalate) – tissue.

Release liner (on the front covering the adhesive matrix containing buprenorphine) (to be removed before applying the patch):

Poly(Ethyleneterephthalate) – foil, siliconised, coated on one side with aluminium.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Sealed child resistant sachet, composed of identical top and bottom layers of heat-sealable laminate, comprising (from outside to inside) paper, PET, polyethylene-based copolymer, aluminium and poly(acrylic acid-co-ethylene).

Pack Sizes: 1, 2, 3, 4, 5, 8, 10 and 12 transdermal patches.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

The patch should not be used if the seal is broken.

Disposal after use:

When changing the patch, the used patch should be removed, the adhesive layer folded inwards on itself, and the patch disposed of safely and out of sight and reach of children.

7 MARKETING AUTHORISATION HOLDER

Qdem Pharmaceuticals Limited
Cambridge Science Park
Milton Road
Cambridge
CB4 0GW
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 40431/0026

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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