SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Buplast 52.5 micrograms/h transdermal patches

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each transdermal patch contains 30 mg buprenorphine.

Area containing the active substance: 37.5 cm2

Nominal release rate: 52.5 micrograms of buprenorphine per hour (over a period of 96 hours).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch

Rectangular beige coloured patch with rounded edges and imprinted with “Buprenorphin” and “52.5 µg/h” in blue colour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Moderate to severe cancer pain and severe pain which does not respond to non-opioid analgesics.

Buplast is not suitable for the treatment of acute pain.

4.2 Posology and method of administration

Posology

Patients over 18 years of age

The dose should be adapted to the condition of the individual patient (pain intensity, suffering, individual reaction) and checked at regular intervals. The lowest possible

dose providing adequate pain relief should be given. Three transdermal patch strengths are available to provide such adaptive treatment: Buplast 35 micrograms/h, Buplast 52.5 micrograms/h and Buplast 70 micrograms/h.

Initial dose selection: patients who have previously not received any analgesics should start with the lowest transdermal patch strength (Buplast 35 micrograms/h). Patients previously given a WHO step-I analgesic (non-opioid) or a step-II analgesic (weak opioid) should also begin with Buplast 35 micrograms/h. According to the WHO recommendations, the administration of a non-opioid analgesic can be continued, depending on the patient's overall medical condition.

When switching from a step-III analgesic (strong opioid) to Buplast and choosing the initial transdermal patch strength, the nature of the previous medicinal product, administration and the mean daily dose should be taken into account in order to avoid the recurrence of pain. In general it is advisable to titrate the dose individually, starting with the lowest transdermal patch strength (Buplast 35 micrograms/h). Clinical experience has shown that patients who were previously treated with higher daily doses of a strong opioid (in the dimension of approximately 120 mg oral morphine) may start the therapy with the next higher transdermal patch strength (see also section 5.1).

To allow for individual dose adaptation in an adequate time period sufficient supplementary immediate release analgesics should be made available during dose titration.

After application of the first Buplast transdermal patch the buprenorphine serum concentrations rise slowly both in patients who have been treated previously with analgesics and in those who have not. Therefore initially, there is unlikely to be a rapid onset of effect. Consequently, a first evaluation of the analgesic effect should only be made after 24 hours.

The previous analgesic medicinal product (with the exception of transdermal opioids) should be given in the same dose during the first 12 hours after switching to Buplast and appropriate rescue medicinal products on demand in the following 12 hours.

Dose titration and maintenance therapy

Buplast should be replaced after 96 hours (4 days) at the latest. For convenience of use, the transdermal patch can be changed twice a week at regular intervals, e.g. always on Monday morning and Thursday evening. The dose should be titrated individually until analgesic efficacy is attained. If analgesia is insufficient at the end of the initial application period, the dose may be increased, either by applying more than one transdermal patch of the same strength or by switching to the next transdermal patch strength. At the same time no more than two transdermal patches regardless of the strength should be applied. If a patch falls off before it needs changing, the transdermal patch should not be used again. A new patch should be applied straight away.

Before application of the next Buplast strength the amount of total opioids administered in addition to the previous transdermal patch should be taken into consideration, i.e. the total amount of opioids required, and the dosage adjusted accordingly. Patients requiring a supplementary analgesic (e.g. for breakthrough pain) during maintenance therapy may take for example 0.2 mg - 0.4 mg buprenorphine sublingual every 24 hours in addition to the transdermal patch. If the regular addition

of 0.4 – 0.6 mg sublingual buprenorphine is necessary, the next strength should be used.

Treatment goals and discontinuation

Before initiating treatment with [<invented name>], 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 [<invented name>], 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).

Duration of administration
Buplast should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with Buplast 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.

Discontinuation of Buplast
After removal of Buplast 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 Buplast is to be followed by other opioids. As a general rule, a subsequent opioid should not be administered within 24 hours after removal of Buplast. For the time being only limited information is available on the starting dose of other opioids administered after discontinuation of Buplast.

Elderly patients
No dosage adjustment of Buplast is required for elderly patients.

Patients with renal insufficiency
See section 4.4.

Patients with hepatic insufficiency
See section 4.4.

Paediatric population

As buprenorphine transdermal patch has not been studied in patients under 18 years of age, the use of the medicinal product in patients below this age is not recommended.

Method of administration
For transdermal use.

Buplast should be applied to non-irritated, clean skin on a non-hairy flat surface, but not to any parts of the skin with large scars. Preferable sites on the upper body are: upper back or below the collar-bone on the chest. Any remaining hairs should be cut off with a pair of scissors (not shaved). If the site of application requires cleansing, this should be done with water. Soap or any other cleansing agents should not be

used. Skin preparations that might affect adhesion of the transdermal patch to the area selected for application of Buplast should be avoided.

The skin must be completely dry before application. Buplast is to be applied immediately after removal from the sachet. Following removal of the release liner, the transdermal patch should be pressed firmly in place with the palm of the hand for approximately 30 seconds. The transdermal patch will not be affected when bathing, showering or swimming.

Buplast should be worn continuously for up to 4 days. After removal of the previous transdermal patch a new Buplast transdermal patch should be applied to a different skin site. At least one week should elapse before a new transdermal patch is applied to the same area of skin.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in 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.
- pregnancy (see section 4.6)

4.4 Special warnings and precautions for use

Tolerance and opioid use disorder (abuse and dependence)

Tolerance, physical and psychological dependence, and opioid use disorder (OUD) may develop upon repeated administration of opioids such as [product name]. Repeated use of [product name] 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 [<invented name>] 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 [<invented name>] 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.

Buprenorphine must only be used with particular caution in acute alcohol intoxication, convulsive disorders, in patients with head injury, shock, a reduced level of consciousness of uncertain origin, increased intracranial pressure without the possibility of ventilation.

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:
Concomitant use of Buplast 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 Buplast 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).

Buprenorphine has a substantially lower dependence liability than pure opioid agonists. In healthy volunteer and patient studies with buprenorphine, withdrawal reactions have not been observed. However, after long-term use of buprenorphine withdrawal symptoms, similar to those occurring during opiate withdrawal, cannot be entirely excluded (see section 4.8). These symptoms are: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal disorders.

In patients abusing opioids, substitution with buprenorphine may prevent withdrawal symptoms. This has resulted in some abuse of buprenorphine and caution should be exercised when prescribing it to patients suspected of having drug abuse problems.

Hepatic impairment
Buprenorphine is metabolised in the liver. The intensity and duration of effect may be altered in patients with liver function disorders. Therefore such patients should be carefully monitored during buprenorphine treatment.

Renal impairment
Since the pharmacokinetics of buprenorphine is not altered during the course of renal failure, its use in patients with renal insufficiency, including dialysis patients, is possible.

Athletes should be aware that this medicine may cause a positive reaction to sports doping control tests.

Patients with fever / external heat

Fever and the presence of heat may increase the permeability of the skin. Theoretically in such situations buprenorphine serum concentrations may be raised during buprenorphine treatment. Therefore on treatment with buprenorphine, attention should be paid to the increased possibility of opioid reactions in febrile patients or those with increased skin temperature due to other causes.

The transdermal patch should not be exposed to excessive heat (e.g. sauna, infrared-radiation).

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.

Serotonin syndrome

Concomitant administration of [<invented name>] 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.

4.5 Interaction with other medicinal products and other forms of interaction

On administration of MAO inhibitors in the last 14 days prior to the administration of the opioid pethidine, life-threatening interactions have been observed affecting the central nervous system and respiratory and cardiovascular function. The same interactions between MAO inhibitors and buprenorphine cannot be ruled out (see section 4.3).

Buplast 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).

Sedative medicines such as benzodiazepines or related drugs, other opioids, anaesthetics, hypnotics, antidepressants, neuroleptics, and in general, medicinal products that depress respiration and the central nervous system:

The concomitant use of Buplast with gabapentinoids (gabapentin and pregabalin) may result in sedation, respiratory depression, hypotension, coma and death.

Concomitant administration of buprenorphine with anticholinergics or medications with anticholinergic activity (e.g. tricyclic antidepressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects.
Administered together with inhibitors or inducers of CYP 3A4 the efficacy of buprenorphine may be intensified (inhibitors) or weakened (inducers).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of buprenorphine in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Towards the end of pregnancy high doses of buprenorphine may induce respiratory depression in the new-born infant even after a short period of administration. Chronic administration of buprenorphine during the last three months of pregnancy may cause a withdrawal syndrome in the new-born infant.
Therefore administration of Buplast is contraindicated during pregnancy.

Breast-feeding
Buprenorphine is excreted in human milk. Studies in rats have shown that buprenorphine can inhibit lactation.
Buplast should not be used during breast-feeding.

Fertility
An effect of buprenorphine on human fertility is unknown. Buprenorphine did not affect fertility in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Buprenorphine has major influence on the ability to drive and use machines. Even when used according to instructions, buprenorphine 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 at the beginning of treatment, at any change of dose and when buprenorphine is used in conjunction with other centrally acting substances including alcohol, tranquillisers, sedatives and hypnotics.

Patients who are affected (e.g. feeling dizzy or drowsy or experience blurred or double vision) should not drive or use machines while using buprenorphine and for at least 24 hours after the patch has been removed.

Patients stabilised on a specific dose will not necessarily be restricted if the above mentioned symptoms are not present.

4.8 Undesirable effects

The following adverse reactions were reported after administration of buprenorphine transdermal patch in clinical studies and from post marketing surveillance.

The frequencies are given as follows:
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 data)

The most commonly reported systemic adverse reactions were nausea and vomiting. The most commonly reported local adverse reactions were erythema and pruritus.

Immune system disorders	
Very rare	Serious allergic reactions
Metabolism and nutrition disorders	
Rare	Appetite lost
Psychiatric disorders	
Uncommon	Confusion, sleep disorder, restlessness
Rare	Psychotomimetic effects (e.g. hallucinations, anxiety, nightmares), decreased libido
Very rare	Dependence, mood swings
Nervous system disorders	
Common	Dizziness, headache
Uncommon	Sedation, somnolence
Rare	Concentration impaired, speech disorder, numbness, dysequilibrium, paraesthesia (e.g. pricking or burning skin sensation)
Very rare	Muscle fasciculation, parageusia
Eye disorders	
Rare	Visual disturbance, blurring of vision, eyelid oedema
Very rare	Miosis
Ear and labyrinth disorders	
Very rare	Ear pain
Vascular disorders	
Uncommon	Circulatory disorders (such as hypotension or, rarely, even circulatory collapse)
Rare	Hot flushes
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea

Rare	Respiratory depression
Very rare	Hyperventilation, hiccups
Gastrointestinal disorders	
Very common	Nausea
Common	Vomiting, constipation
Uncommon	Dry mouth
Rare	Pyrosis
Very rare	Retching
Skin and subcutaneous tissue disorders	
Very common	Erythema, pruritus
Common	Exanthema, diaphoresis
Uncommon	Rash
Rare	Urticaria
Very rare	Pustules, vesicles
Not Known	dermatitis contact, application skin discolouration
Renal and urinary disorders	
Uncommon	Urinary retention, micturition disorders
Reproductive system and breast disorders	
Rare	Decreased erection
General disorders and administration site conditions	
Common	Oedema, tiredness
Uncommon	Weariness
Rare	Withdrawal symptoms, administration site reactions
Very rare	Thoracic pain

Drug dependence
Repeated use of buprenorphine 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).

In some cases delayed allergic reactions occurred with marked signs of inflammation. In such cases treatment with buprenorphine should be terminated.

Buprenorphine has a low risk of dependence. After discontinuation of buprenorphine, withdrawal symptoms are unlikely. This is due to the very slow dissociation of buprenorphine from the opiate receptors and to the gradual decrease of buprenorphine serum concentrations (usually over a period of 30 hours after removal of the last transdermal patch). However, after long-term use of buprenorphine withdrawal symptoms, similar to those occurring during opiate withdrawal, cannot be entirely excluded.
These symptoms include: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastro-intestinal disorders.

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 or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Buprenorphine has a wide safety margin. Due to the rate-controlled delivery of small amounts of buprenorphine into the blood circulation high or toxic buprenorphine concentrations in the blood are unlikely. The maximum serum concentration of buprenorphine after the application of the buprenorphine 70 micrograms/h transdermal patch is about six times less than after the intravenous administration of the therapeutic dose of 0.3 mg buprenorphine.

Symptoms
In principal, on overdose with buprenorphine, symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These are: respiratory depression, sedation, somnolence, nausea, vomiting, cardiovascular collapse, and marked miosis.

Treatment
General emergency measures apply. The airway should be kept open (aspiration!), Respiration and circulation should be maintained, depending on the symptoms. Naloxone has a limited impact on the respiratory depressant effect of buprenorphine. High doses are needed given either as repeated boluses or infusion (for example starting with a bolus administration of 1-2 mg intravenously. Having attained an adequate antagonistic effect, administration by infusion is recommended to maintain constant naloxone plasma levels). Therefore, adequate ventilation should be established.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioids, Oripavine derivatives
ATC code: N02AE01

Mechanism of action
Buprenorphine is a strong opioid with agonistic activity at the mu-opioid receptor and antagonistic activity at the kappa-opioid receptor. Buprenorphine appears to have the general characteristics of morphine, but has its own specific pharmacology and clinical attributes.

In addition, numerous factors, e.g. indication and clinical setting, route of administration and the interindividual variability, have an impact on analgesia and therefore have to be considered when comparing analgesics.

Clinical efficacy and safety
In daily clinical practice different opioids are ranked by a relative potency, although this is to be considered a simplification.

The following 24 – hour oral doses of morphine are considered to be approximately equivalent to the buprenorphine patches shown, however when switching due to possible opioid-induced hyperalgesia, reduce the calculated equivalent dose of the new opioid by one-quarter to one-half.

Buprenorphine patches are approximately equivalent to the following 24-hour doses of oral morphine

Morphine salt 84mg daily = buprenorphine 35 micrograms transdermal patches 4-day patches

Morphine salt 126mg daily = buprenorphine 52.5 micrograms transdermal patches 4-day patches

Morphine salt 168mg daily = buprenorphine 70 micrograms transdermal patches 4-day patches

Adverse reactions are similar to those of other strong opioid analgesics. Buprenorphine appears to have a lower dependence liability than morphine.

5.2 Pharmacokinetic properties

Absorption
After application, buprenorphine is absorbed through the skin. The continuous delivery of buprenorphine into the systemic circulation is by controlled release from the adhesive polymer-based matrix system

Distribution
Buprenorphine has a plasma protein binding of about 96%.

After the initial application of buprenorphine the plasma concentrations of buprenorphine gradually increase, and after 12-24 h the plasma concentrations reach the minimum effective concentration of 100 pg/ml. From the studies performed with the buprenorphine 35 micrograms/h in healthy volunteers, an average Cmax of 200 to 300 pg/ml and an average tmax of 60-80 h were determined. In one volunteer study, buprenorphine 35 micrograms/h and buprenorphine 70 micrograms/h were applied in a cross-over design. From this study, dose proportionality for the different strengths was demonstrated.

Biotransformation
Buprenorphine is metabolised in the liver to N-dealkylbuprenorphine (norbupren-orphine) and to glucuronide conjugated metabolites. 2/3 of the active substance is eliminated unchanged in the faeces and 1/3 eliminated as conjugates of unchanged or dealkylated buprenorphine via the urinary system. There is evidence of enterohepatic recirculation.

Elimination

After removal of buprenorphine transdermal patch the plasma concentrations of buprenorphine steadily decrease and are eliminated with a half-life of approx. 30 hours (range 22 - 36). Due to the continuous absorption of buprenorphine from the depot in the skin elimination is slower than after intravenous administration.

5.3 Preclinical safety data

Standard toxicological studies have not provided evidence of any particular potential risks for humans. In studies with repeated application of buprenorphine in rats a reduced increase in body weight was observed.

Studies on fertility and general reproductive capacity in rats showed no detrimental effects. Studies in rats and rabbits provided evidence for fetotoxicity and an increased post-implantation loss, although only at maternal toxic doses.

Studies in rats showed an impaired intra-uterine growth, delays in the development of certain neurological functions and high peri/post natal mortality in neonates after treatment of the dams during gestation or lactation. There is evidence that complications during delivery and reduced lactation contributed to these effects. There was no evidence of embryotoxicity including teratogenicity in rats or rabbits.

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.

In vitro and *in vivo* evaluations on the mutagenic potential of buprenorphine did not indicate any clinically relevant effects.

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

Toxicological data available did not indicate a sensitising potential of the excipients used in the transdermal patches.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Adhesive matrix (containing buprenorphine): povidone K90, levulinic acid, oleyl oleate, poly[acrylic acid-co-butylacrylate-co-(2-ethylhexyl)acrylate-co-vinylacetate] (5:15:75:5)

Adhesive matrix (without buprenorphine): poly[(2-ethylhexyl)acrylate-co-glycidylmethacrylate-co-(2-hydroxyethyl)acrylate-co-vinylacetate] (68:0,15:5:27)

Separating foil between adhesive matrices with and without buprenorphine: polyethylene terephthalate film

Backing foil: polyester

Release liner (on the front covering the adhesive matrix containing buprenorphine): polyethylene terephthalate film, siliconised

blue printing ink

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Each child-proof sachet is made of a composite layer material consisting of Paper/ PET/ PE/ Aluminium/ Surlyn. One sachet contains one transdermal patch.

Pack sizes:
Packs containing 3, 4, 5, 8, 10, 16 or 20 sachets individually sealed transdermal patches.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Used transdermal patches should be folded in half, with the adhesive side inwards, placed in the original sachet and discarded safely, or whenever possible returned to the pharmacy. Any used or unused transdermal patches should be disposed of in accordance with local requirements or returned to the pharmacy.

7 MARKETING AUTHORISATION HOLDER

GENERICS (UK) LIMITED (T/A) Mylan
Potters Bar
Hertfordshire
EN6 1TL
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 04569/1571

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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