SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Carlosafine 70 micrograms/h transdermal patch
Buprenorphine Glenmark 70 micrograms/h transdermal patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each transdermal patch contains 40 mg buprenorphine.

Area containing the active substance: 50 cm^2

Nominal release rate: 70 micrograms of buprenorphine per hour (over a period of 96 hours).

For the full list of excipients, see section 6.1.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 “70 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.

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

Initial dose selection: patients who have previously not received any analgesics should start with the lowest transdermal patch strength (Buprenorphine 35 micrograms/h). Patients previously given a WHO step-I analgesic (non-opioid) or a step-II analgesic (weak opioid) should also begin with Buprenorphine 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 Buprenorphine 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 (Buprenorphine 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.

The necessary strength of Buprenorphine must be adapted to the requirements of the individual patient and checked at regular intervals.

After application of the first Buprenorphine 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 Buprenorphine and appropriate rescue medicinal products on demand in the following 12 hours.

Dose titration and maintenance therapy

Buprenorphine 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.

Before application of the next Buprenorphine 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 one to two 0.2 mg buprenorphine sublingual tablets 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.

Elderly patients

No dosage adjustment of Buprenorphine is required for elderly patients.

Patients with renal insufficiency

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.

Patients with hepatic insufficiency

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 liver insufficiency should be carefully monitored during treatment with Buprenorphine.

Paediatric population

As Buprenorphine 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

Buprenorphine 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 Buprenorphine should be avoided.

The skin must be completely dry before application. Buprenorphine 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. However it should not be exposed to excessive heat (e.g., sauna, infra-red radiation)

Buprenorphine should be worn continuously for up to 4 days. After removal of the

previous transdermal patch a new Buprenorphine 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.

Duration of administration
Buprenorphine should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with Buprenorphine 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 Buprenorphine
After removal of Buprenorphine 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 Buprenorphine is to be followed by other opioids. As a general rule, a subsequent opioid should not be administered within 24 hours after removal of Buprenorphine. For the time being only limited information is available on the starting dose of other opioids administered after discontinuation of Buprenorphine.

4.3 Contraindications

Carlosafine is contraindicated in

- 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

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.

Buprenorphine occasionally causes respiratory depression. Therefore care should be taken when treating patients with impaired respiratory function or patients receiving medicinal products which can cause respiratory depression.

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.

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.

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

Risk from concomitant use of sedative medicines such as benzodiazepines or related drugs:

Concomitant use of Carlosafine 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 Carlosafine 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).

Serotonin syndrome

Concomitant administration of Carlosafine and other serotonergic agents, such as MAO inhibitors, 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.

Paediatric population

As Buprenorphine 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.

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).

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).

When buprenorphine is applied together with other opioids, anaesthetics, hypnotics, sedatives, antidepressants, neuroleptics, and in general, medicinal products that depress respiration and the central nervous system, the CNS effects may be intensified. This applies also to alcohol.

Administered together with inhibitors or inducers of CYP 3A4 the efficacy of buprenorphine may be intensified (inhibitors) or weakened (inducers).

Sedative medicines such as benzodiazepines or related drugs:

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).

Co-administration of serotonergic medicinal products, such as MAO inhibitors, 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).

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 neonate even after a short period of administration. Long-term administration of buprenorphine during the last three months of pregnancy may cause a withdrawal syndrome in the new-born infant.
Therefore Buprenorphine is contraindicated during pregnancy.

Breast-feeding
Buprenorphine is excreted in human milk. In rats buprenorphine has been found to inhibit lactation.
Buprenorphine should not be used during lactation.

Fertility
An effect of buprenorphine on fertility in animals is not known (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 dosage 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 dosage will not necessarily be restricted if the above mentioned symptoms are not present.

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:
    -
    - o The medicine has been prescribed to treat a medical or dental problem; and
    - o 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

The following adverse reactions were reported after administration of buprenorphine in clinical studies and from postmarketing 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)

a) The most commonly reported systemic adverse reactions were nausea and vomiting.
b) 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

Cardiac/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

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

* see section c)

c) 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 Website: 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. Keep the airway open (aspiration!), maintain respiration and circulation, 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

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.

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

The relative potency of buprenorphine in different application forms and in different clinical settings has been described in literature as follows:

- Morphine p.o.: BUP i.m. as 1 : 67 - 150 (single dose; acute pain model)
- Morphine p.o.: BUP s.l. as 1 : 60 - 100 (single dose, acute pain model; multiple dose, chronic pain, cancer pain)
- Morphine p.o.: BUP TTS as 1 : 75 - 115 (multiple dose, chronic pain)

Abbreviations:

p.o = oral; i.m. = intramuscular; s.l. = sublingual; TTS = transdermal; BUP = buprenorphine

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

General characteristics of the active substance

Buprenorphine has a plasma protein binding of about 96%.

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.

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.

Characteristics of buprenorphine in healthy volunteers

After the application of Buprenorphine, 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.

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 C_{max} of 200 to 300 pg/ml and an average t_{max} 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.

After removal of Buprenorphine 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 shown evidence of any particular potential risks for humans. In tests with repeated doses of buprenorphine in rats the increase in body weight was reduced.

Studies on fertility and general reproductive capacity of rats showed no detrimental effects. Studies in rats and rabbits revealed signs of fetotoxicity and increased post-implantation loss.

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

In vitro and *in vivo* examinations 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 additives ofthe 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 4, 5, 8, 10, 16 or 20 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

Glenmark Pharmaceuticals Europe Limited
Laxmi House
2B Draycott Avenue
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HA3 0BU

8 MARKETING AUTHORISATION NUMBER(S)

PL 25258/0173

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