Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Prenopatch 10 microgram/hour transdermal patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each transdermal patch contains 10 mg of buprenorphine in a 12.5 cm^2 area releasing a nominal 10 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

Rectangular beige coloured patch with rounded edges and imprinted with “Buprenorphin” and “10 µg/h” in blue colour.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

Prenopatch is not suitable for the treatment of acute pain.

Prenopatch is indicated in adults.

4.2 Posology and method of administration

Posology
Patients aged 18 years and over:

The lowest Prenopatch dose (Prenopatch 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.

Titration

During initiation of treatment with Prenopatch, short-acting supplemental analgesics may be required (see section 4.5) as needed until analgesic efficacy with Prenopatch is attained.

The dose of Prenopatch may be titrated upwards as indicated after 3 days, when the maximum effect of a given dose is established. Subsequent dose 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 buprenorphine. 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.

Prenopatch should be administered every 7th day.

Duration of administration

Prenopatchshould under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with Prenopatch 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

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 Prenopatch 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).

Conversion from opioids

Prenopatch can be used as an alternative to treatment with other opioids. Such patients should be started on the lowest available dose (Prenopatch 5 microgram/hour transdermal patch) and continue taking short-acting supplemental analgesics (see section 4.5) during titration, as required.

Special populations

Elderly

No dosage adjustment of Prenopatch is required in elderly patients.

Renal impairment

No special dose adjustment of Prenopatch 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 Prenopatch.

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

Paediatric population

The safety and efficacy of Prenopatch in children and adolescents below 18 years of age has not been established. No data are available.

Method of administration

Prenopatch is for transdermal use.

The patch must not be divided or cut into pieces.
The patch should not be used if the seal is broken.

Patch application

Prenopatch 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. Prenopatch 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. Prenopatch 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.

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.

4.4 Special warnings and precautions for use

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

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

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.

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

Buprenorphine 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.

Controlled human and animal studies indicate that buprenorphine has a lower dependence liability than pure agonist analgesics. In humans limited euphorigenic effects have been observed with buprenorphine. This may result in some abuse of the medicinal product and caution should be exercised when prescribing to patients known to have, or suspected of having, a history of drug abuse or alcohol abuse or serious mental illness.

Chronic use of buprenorphine can result in the development of physical dependence. Withdrawal (abstinence syndrome), when it occurs, is generally mild, begins after 2 days and may last up to 2 weeks. Withdrawal symptoms include agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal disorders.

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

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, 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.

4.5 Interaction with other medicinal products and other forms of interaction

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

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 buprenorphine with ketoconazole as compared to buprenorphine alone.

The interaction between buprenorphine and CYP3A4 enzyme inducers has not been studied.
Co-administration of buprenorphine 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:

Buprenorphine should be used cautiously with:

Other central nervous system depressants: other opioid derivatives (analgesics and antitussives containing e.g. morphine, dextropropoxyphene, codeine, dextromethorphan or noscapine). Certain antidepressants, sedative H1-receptor antagonists, alcohol, anxiolytics, neuroleptics, clonidine and related substances. These combinations increase the CNS depressant activity. Benzodiazepines: This combination can potentiate respiratory depression of central origin (see section 4.4).

At typical analgesic doses buprenorphine is described to function as a pure mu receptor agonist. In buprenorphine clinical studies subjects receiving full mu agonist opioids (up to 90 mg oral morphine or oral morphine equivalents per day) were transferred to buprenorphine. There were no reports of abstinence syndrome or opioid withdrawal during conversion from entry opioid to buprenorphine (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of 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 neonate.

Therefore buprenorphine should not be used during pregnancy and in women of childbearing potential who are not using effective contraception.

Breastfeeding
Buprenorphine is excreted in human milk. Studies in rats have shown that buprenorphine may inhibit lactation. Available pharmacodynamic/toxicological data in animals has shown excretion of buprenorphine in milk (see

section 5.3). Therefore the use of buprenorphine 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

Buprenorphine has a 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 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 undesirable effects (e.g. dizziness, drowsiness, blurred vision) during treatment initiation or titration to a higher dose should not drive or use machines, for at least 24 hours after the patch has been removed.

4.8 Undesirable effects

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

The following undesirable effects have occurred:

System organ class MedDRA	Very common (≥1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥1/10,000 to <1/1000)	Very rare (<1/10,000)	Not known (cannot be estimated from the available data)
Immune system disorders			Hypersensitivity	Anaphylactic reaction		Anaphylactoid reaction
Metabolic and nutritional disorders		Anorexia		Dehydration		
Psychiatric disorders		Confusion, Depression, Insomnia, Nervousness, Anxiety	Sleep disorder, Restlessness, Agitation, Euphoric mood, Affect liability, Hallucinations, Nightmares, Decreased libido	Psychotic disorder	Drug dependence, Mood swings	Depersonalisation
Nervous system disorders	Headache, Dizziness, Somnolence	Tremor	Sedation, Dysgeusia, Dysarthria, Hypoaesthesia, Memory impairment, Migraine, Syncope, Abnormal co-ordination, Disturbance in	Balance disorder, Speech disorder	Involuntary muscle contractions	Convulsions

			attention, Paraestheia			
Eye disorders			Dry eye, Blurred vision	Visual disturbance, Eyelid oedema, Miosis		
Ear and labyrinth disorders			Tinnitus,Vertigo		Ear pain	
Cardiac disorders			Palpitations, Tachycardia	Angina pectoris		
Vascular disorders			Hypotension, Circulatory collapse, Hypertension, Flushing	Vasodilatation, Orthostatic hypotension		
Respiratory, thoracic and mediastinal disorders		Dyspnoea	Cough, Wheezing, Hiccups	Respiratory depression, Respiratory failure, Asthma aggravated, Hyperventilation, Rhinitis		
Gastrointestinal disorders	Constipation, Nausea, Vomiting	Abdominal pain, Diarrhoea, Dyspepsia, Dry mouth	Flatulence	Dysphagia, Ileus		Diverticulitis
Hepatobiliary disorders						Biliary colic
Skin and subcutaneous tissue disorders	Pruritus, Erythema	Rash, Sweating, Exanthema	Dry skin, Urticaria, Dermatitis contact	Face oedema	Pustules, Vesicles	
Musculoskeletal and connective tissue disorders		Muscular weakness	Myalgia, Muscle spasms			
Renal and urinary disorders			Urinary retention, Micturition disorder			
Reproductive system and breast disorders				Erectile dysfunction, Sexual dysfunction		
General disorders and administration site conditions	Application site reaction[1]	Tiredness, Asthenic conditions, Peripheral oedema	Fatigue, Pyrexia, Rigors, Oedema, Drug withdrawal syndrome, Application site dermatitis*, Chest pain	Influenza like illness		
Investigations			Alanine			

			aminotransferase increased, Weight decreased			
Injury, poisoning and procedural complications			Accidental injury, Fall			

* In some cases delayed local allergic reactions occurred with marked signs of inflammation. In such cases treatment with buprenorphine should be terminated.
[1] Includes application site erythema, application site oedema, application site pruritus, application site rash.

Buprenorphine has a low risk of physical dependence. After discontinuation of buprenorphine, withdrawal symptoms are unlikely. 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). However, after long-term use of buprenorphine, withdrawal symptoms similar to those occurring during opioid withdrawal, cannot be entirely excluded. These symptoms include agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal 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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

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.
Treatment: Any patches should be removed from the patient's skin. A patent airway should be established and maintained, respiration should be assisted or controlled as indicated and adequate body temperature and fluid balance should be maintained. 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 μ-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, oripavine derivatives;
ATC code: N02AE01

Buprenorphine is a partial 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. Buprenorphine 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 buprenorphine, buprenorphine concentrations decline, decreasing approximately 50% in 12 hours (range 10–24 h).

Absorption:

Following buprenorphine application, buprenorphine diffuses from the patch through the skin. In clinical pharmacology studies, the median time for "buprenorphine 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 buprenorphine 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 buprenorphine 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 buprenorphine 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 430 l, 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 buprenorphine 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 551/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 buprenorphine 20µg/h transdermal patch. The effect on metabolism catalysed by CYP2C8, CYP2C9 and CYP2C19 has not been studied.

5.3 Preclinical safety data

Systemic toxicity and dermal toxicity
In single- and repeat-dose toxicity studies in rats, rabbits, guinea pigs, dogs and minipigs, buprenorphine 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.

Reproductive and development 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.

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: poly(ethylene terephthalate) film

Backing foil: polyester

Release liner: poly(ethylene terephthalate) film, siliconised

blue printing ink

6.2 Incompatibilities

Not applicable

6.3 Shelf life

21 months

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Each child-proof sachet is made of a composite layer material consisting of Paper/ PET/ PE/ Aluminium/ Poly (acrylic acid-co-ethylene) (=Surlyn). One sachet contains one transdermal patch.

Packs containing 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 18, 20 or 24 individually sealed transdermal patches.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7 MARKETING AUTHORISATION HOLDER

Clonmel Healthcare Ltd
Waterford Road
Clonmel
Co. Tipperary
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0126/304/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th July 2017

10 DATE OF REVISION OF THE TEXT

November 2017