SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Panitaz 10 micrograms/h Transdermal Patches

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each transdermal patch contains 10 mg buprenorphine.
Area containing active substance: 12.5 cm^2.
Nominal release rate: 10 micrograms per hour (over a period of 7 days).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch

Rectangular patch with rounded edges, a beige coloured web backing layer imprinted with ñBuprenorphinò and ñ10 ε g/hò in blue colour, a transparent adhesive matrix laminated with a central placed transparent matrix and a transparent release liner with a cut to facilitate the application.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Panitaz is not suitable for the treatment of acute pain.

4.2 Posology and method of administration

Posology
Panitaz should be administered every 7^{th} day.

Patients aged 18 years and over:
The lowest Panitaz dose (Panitaz 5 micrograms/h 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 and titration with Panitaz, patients should use the usual recommended doses of short-acting supplemental analgesics (see section 4.5) as needed until analgesic efficacy with Panitaz is attained.

The dose should not be increased before 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 patientôs 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, regardless of the patch strength. 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:
Panitaz can be used as an alternative to treatment with other opioids. Such patients should be started on the lowest available dose (Panitaz 5 micrograms/h transdermal patch) and continue taking short-acting supplemental analgesics (see section 4.5) during titration, as required.

Patients under 18 years of age:
As Panitaz has not been studied in patients under 18 years of age the use of Panitaz in patients below this age is not recommended.

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

Renal impairment:
No special dose adjustment of Panitaz 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 Panitaz.

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

Method of administration

Panitaz is for transdermal use.

Patch application:
Panitaz 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. Panitaz 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. Panitaz 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.

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.

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

4.3 Contraindications

Panitaz is contraindicated in:

- patients with known hypersensitivity to the active substance buprenorphine or to any of the excipients (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

Panitaz should be used with particular caution in patients with convulsive disorders, 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).

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.

Panitaz 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 product and caution should be exercised when prescribing to patients known to have, or suspected of having, a history of drug abuse.

As with all opioids, 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.

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

Panitaz 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.

A drug interaction study 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:
Panitaz should be used cautiously with:

Benzodiazepines: This combination can potentiate respiratory depression of central origin, with risk of death in case of overdose (see section 4.4).

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.

Buprenorphine is a partial mu-receptor agonist but it is described to function as a pure mu receptor agonist at typical analgesic doses. These doses produce buprenorphine exposures comparable to or greater than those produced by buprenorphine 5, 10, and 20 micrograms/h transdermal patches. In buprenorphine clinical studies, where 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 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 Panitaz should not be used during pregnancy and in women of childbearing potential who are not using effective contraception.

Breastfeeding
Studies in rats have shown that buprenorphine may inhibit lactation. Excretion of buprenorphine into the milk in rats has been observed. Data on excretion into human milk are not available. Therefore the use of Panitaz during lactation should be avoided.

4.7 Effects on ability to drive and use machines

Panitaz has a major influence on the ability to drive and use machines. Even when used according to instructions, Panitaz may affect the patientôs 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.

In patients who are affected, such as during treatment initiation or titration to a higher dose, these patients 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 patientôs 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:

- ñThe 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 óstatutory defenceô).

- 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).ò

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 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:

Very common (Ó1/10), common (Ó1/100, <1/10), uncommon (Ó1/1000, <1/100), rare (Ó1/10,000, <1/1000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Immune system disorders

Uncommon	hypersensitivity
Very rare	anaphylactic reaction, anaphylactoid reactions

Metabolism and nutrition disorders

Common	anorexia
Uncommon	dehydration

Psychiatric disorders

Common	confusion, depression, insomnia, nervousness
Uncommon	sleep disorder, restlessness, agitation, depersonalisation, euphoric mood, affect lability, anxiety, hallucinations, nightmares
Rare	psychotic disorders, decreased libido
Very rare	drug dependence, mood swings

Nervous system disorders

Very common	headache, dizziness, somnolence
Common	paraesthesia
Uncommon	sedation, dysgeusia, dysarthria, hypoaesthesia, memory impairment, migraine, syncope, tremor, abnormal co-ordination, disturbance in attention
Rare	balance disorder, speech disorder
Very rare	involuntary muscle contractions

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	angina pectoris, palpitations, tachycardia

Vascular disorders

Common	vasodilatation
Uncommon	hypotension, circulatory collapse, hypertension, flushing

Respiratory, thoracic and mediastinal disorders

Common	dyspnoea
Uncommon	asthma aggravated, cough, hypoxia, rhinitis, wheezing, hyperventilation, hiccups
Rare	respiratory depression, respiratory failure

Gastrointestinal disorders

Very common	constipation, dry mouth, nausea, vomiting
Common	abdominal pain, diarrhoea, dyspepsia
Uncommon	flatulence
Rare	diverticulitis, dysphagia, ileus

Hepatobiliary disorders

Rare	biliary colic

Skin and subcutaneous tissue disorders

Very common	pruritus, erythema
Common	rash, sweating, exanthema
Uncommon	dry skin, face oedema, urticaria
Very rare	pustules, vesicles

Musculoskeletal and connective tissue disorders

Uncommon	muscle cramp, myalgia, muscular weakness, muscle spasms

Renal and urinary disorders

Uncommon	urinary retention, micturition disorders

Reproductive system and breast disorders

Rare	erectile dysfunction, sexual dysfunction

General disorders and administration site conditions

Very common	application site pruritus, application site reaction
Common	tiredness, asthenia, pain, peripheral oedema, application site erythema, application site rash, chest pain
Uncommon	fatigue, influenza-like illness, pyrexia, rigors, malaise, oedema, drug withdrawal syndrome
Rare	application site inflammation*

Investigations

Uncommon	alanine aminotransferase increased, weight decreased

Injury, poisoning and procedural complications

Uncommon	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.

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 the Yellow Card Scheme, website: 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.

Treatment:
Remove any patches from the patientôs 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. The dose of naloxone may be in the range 5 to 12 mg intravenously. The onset of the naloxone effect may be delayed by 30 minutes or more. Maintenance of adequate ventilation is more important than treatment with naloxone.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Analgesics, opioids; 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 five 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 ï 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 10ï 24 h).

Absorption:
Following buprenorphine application, buprenorphine diffuses from the patch through the skin. In clinical pharmacology studies, the median time for ñbuprenorphine 10 ε g/hò 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 20ε g/h transdermal patch. The effect on metabolism catalysed by CYP2C8, CYP2C9 and CYP2C19 has not been studied.

5.3 Preclinical safety data

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. No teratogenic effects were observed in rats or rabbits. However, perinatal mortality was reported in the literature for rats treated with buprenorphine.

A standard battery of genotoxicity tests indicated that buprenorphine is non-genotoxic.
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 of 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-glycidylmethacrylat-co-(2-hydroxyethyl)acrylate-co-vinylacetate] (68:27:5:0,15)

Separating foil between adhesive matrices with and without buprenorphine: PET film

Backing web: polyester

Release liner: PET film (to be removed before applying the patch)

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

Type 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 individually sealed 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

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