SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCTS

Prenotrix 70 micrograms/h, transdermal patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Prenotrix 70 micrograms/h transdermal patch:

One 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 72 hours).

Excipient with known effect: soya oil 32 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch

Tan coloured, rectangular transdermal patch with four rounded edges and topped off corners marked:

Prenotrix 35 micrograms/h, transdermal patch: Buprenorphin 70 µg/h

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Prenotrix is not suitable for the treatment of acute pain.

4.2 Posology and method of administration

Posology Patients over 18 years of age

The Prenotrix dosage should be adapted to the condition of the individual patient (pain intensity, suffering, individual reaction). The lowest possible dosage providing adequate pain

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

Initial dose selection

Patients who have previously not received any analgesics should start with the lowest transdermal patch strength Prenotrix 35 micrograms/h. Patients previously given a WHO step-I analgesic (non-opioid) or a step-II analgesic (weak opioid) should also begin with Prenotrix 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 Prenotrix and choosing the initial transdermal patch strength, the nature of the previous medication, 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 (Prenotrix 35 micrograms/h). Clinical experience has shown that patients who were previously treated with higher daily dosages 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 Prenotrix must be adapted to the requirements of the individual patient and checked at regular intervals.

After application of the first Prenotrix 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 medication (with the exception of transdermal opioids) should be given in the same dose during the first 12 hours after switching to Prenotrix and appropriate rescue medication on demand in the following 12 hours.

Dose titration and maintenance therapy

Prenotrix should be replaced after 72 hours (3 days) at the latest. 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 Prenotrix 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 buprenorphine 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.

Paediatric population

As Prenotrix 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.

Elderly patients

No dosage adjustment of Prenotrix 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 Prenotrix.

Method of application

Prenotrix 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 Prenotrix should be avoided.

The skin must be completely dry before application. Prenotrix is to be applied immediately after removal from the sachet. Following removal of the stripfoil, 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, infrared-radiation).

Prenotrix should be worn continuously for up to 3 days. After removal of the previous transdermal patch a new Prenotrix 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.

Treatment goals and discontinuation

Before initiating treatment with Prenotrix, 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 Prenotrix, 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

Prenotrix should not be used longer than necessary. If long-term pain treatment with Prenotrix 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 Prenotrix 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 Prenotrix is to be followed by other opioids. As a general rule, a subsequent opioid should not be administered within 24 hours after removal of Prenotrix. For the time being only limited information is available on the starting dose of other opioids administered after discontinuation of Prenotrix.

4.3 Contraindications

Prenotrix is contraindicated in:

- hypersensitivity to the active substance buprenorphine, soya, peanuts 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 is not recommended for analgesia in the immediate post-operative period *"Do not use for acute post-operative pain owing to the increased risk of persistent post-operative opioid use (PPOU) and opioid-induced ventilatory impairment (OIVI)"*.

Prenotrix 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 Prenotrix, withdrawal reactions have not been observed. However, after long-term use of Prenotrix withdrawal symptoms, similar to those occuring during opiate withdrawal, cannot be entirely excluded (see section 4.8). These symptoms are: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastro-intestinal disorders.

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 Prenotrix. Repeated use of Prenotrix 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 Prenotrix 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 Prenotrix 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

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 Prenotrix treatment.

Athletes should be aware that this medicine may cause a positive reaction to sports

doping control tests.

Paediatric population

As Prenotrix 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 Prenotrix treatment. Therefore on treatment with Prenotrix, attention should be paid to the increased possibility of opioid reactions in febrile patients or those with increased skin temperature due to other causes.

Serotonin syndrome

Concomitant administration of Prenotrix 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.

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 Prenotrix cannot be ruled out (see section 4.3).

When Prenotrix 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.

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

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

Prenotrix should be used cautiously when co-administered with:

- 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).

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data from the use of Prenotrix patches 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 Prenotrix is contraindicated during pregnancy

Breast-feeding

Buprenorphine is excreted in human milk. In rats, buprenorphine has been found to inhibit lactation.

Prenotrix 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

Prenotrix has major influence on the ability to drive and use machines.

Even when used according to instructions, Prenotrix 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 Prenotrix is used in conjunction with other centrally acting substances including alcohol, tranquilizer, 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 Prenotrix for at least 24 hours after the patch has been removed.

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

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 under the influence of this medicine
- However, you would not be committing an offence (called 'statutory defence') if:
    - 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 and;
    - it was not affecting your ability to drive safely

4.8 Undesirable effects

The following adverse reactions were reported after administration of buprenorphine in clinical studies and from post marketing surveillance. The frequencies are given as follows:

Very common (≥1/10)

Common (≥1/100, <1/10)

Uncommon (≥1/1.000, <1/100)

Rare (≥1/10.000, <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

Musculoskeletal, connective tissue and bone disorders

Common: arthralgia

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 Prenotrix should be terminated.

Buprenorphine has a low risk of dependence. After discontinuation of Prenotrix, 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 Prenotrix withdrawal symptoms, similar to those occurring during opiate withdrawal, cannot be entirely excluded. These symptoms include: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal disorders.

Drug dependence

Repeated use of Prenotrix 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).

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 Yellow Card Scheme
[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 Prenotrix 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 prescribed 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

a) General characteristics of the active substance

Buprenorphine has a plasma protein binding of about 96 %.

Buprenorphine is metabolised in the liver to N-dealkylbuprenorphine (norbuprenorphine) 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 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 intra-muscular or oral administration buprenorphine apparently accumulates in the foetal gastrointestinal-lumen – presumably due to biliary excretion, as enterohepatic circulation has not fully developed.

b) Characteristics of buprenorphine patches in healthy volunteers

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

After the initial application of Prenotrix patches the plasma concentrations of buprenorphine gradually increase, and after 4 - 12 h the plasma concentrations reach the minimum effective concentration of 100 pg/ml. From the studies performed with Prenotrix 35 micrograms/h in healthy volunteers an average C_{max} of 273 pg/ml and an average t_{max} of 34 h from studies performed with Prenotrix patches 70 micrograms/h an average C_{max} of 425 pg/ml and an average t_{max} of 29 h were determined. In one volunteer study, buprenorphine patches 35 micrograms/h and buprenorphine patches 70 micrograms/h were applied in a cross-over design. From this study, dose proportionality for the different strengths was demonstrated.

After removal of Prenotrix patches the plasma-concentrations of buprenorphine steadily decrease and are eliminated with a half-life of approx.25 hours (range 24-27). Due to the continuous absorption of buprenorphine from the depot in the skin elimination is 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 postimplantation loss.

Studies in rats showed diminished intra-uterine growth, delays in the development of certain neurological functions and high peri/postnatal 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 of the transdermal patches.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Drug containing adhesive matrix:

styrene-butadiene-styrene (SBS) and styrene-butadiene block co-polymers, colophonium resin, antioxidants (2,4-Bis(1,1-Dimethylethyl)phenyl phosphite (3:1); Tris(2,4-Di-Tert-Butylphenyl)phosphate), aloe vera leaf extract oil (also contains refined soya-bean oil and alpha tocopherol acetate)

Backing foil: pigmented polyethylene and aluminium vapour coated polyester, blue printing colour

Release liner with pull of aid: polyester film, one side siliconised (to be removed prior application)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

18 months.

6.4 Special precautions for storage

Do not store above 25°C

Do not freeze

6.5 Nature and contents of container

Each transdermal patch is covered with a loose siliconised PETP foil cover sheet and is packed individually into a sealed sachet. The sachet is made from PETP/Aluminium/PE. Packs contain 4, 5, 8, 10, 16, 20 or 24 (6 x 4) individually sealed patches.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements

7 MARKETING AUTHORISATION HOLDER

Activase Pharmaceuticals Limited,

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Nicosia.

Cyprus

8 MARKETING AUTHORISATION NUMBER(S)

PL 28444/0132

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