SUMMARY OF PRODUCT CHARACTERISTICS

1. NAAM VAN HET GENEESMIDDEL

Buprenorfine Sandoz 25 microgram/uur 7 dagen, pleister voor transdermaal gebruik
Buprenorfine Sandoz 30 microgram/uur 7 dagen, pleister voor transdermaal gebruik
Buprenorfine Sandoz 40 microgram/uur 7 dagen, pleister voor transdermaal gebruik

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

{[Nationally completed name] 25 microgram/hour transdermal patch}:
Each transdermal patch contains 25 mg of buprenorphine per 31.25 cm^2, releasing 25 micrograms of buprenorphine per hour.
{[Nationally completed name] 30 microgram/hour transdermal patch}:
Each transdermal patch contains 30 mg of buprenorphine per 37.5 cm^2, releasing 30 micrograms of buprenorphine per hour.
{[Nationally completed name] 40 microgram/hour transdermal patch}:
Each transdermal patch contains 40 mg of buprenorphine per 50 cm^2, releasing 40 micrograms of buprenorphine per hour.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal patch.

The medicinal product is composed of a transdermal patch containing the active substance integrated with an oversized pale yellowish-brown cover patch without any active substance. The shape of the transdermal patch is rectangular with rounded edges. The transdermal patch contains the following imprint:
‘Buprenorphinum 25 µg/h’
‘Buprenorphinum 30 µg/h’
‘Buprenorphinum 40 µg/h’

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

[Nationally completed name] is not suitable for the treatment of acute pain.

[Nationally completed name] is indicated in adults.

4.2 Posology and method of administration

Posology
[Nationally completed name] should be administered every 7th day.

Patients aged 18 years and over
The lowest dose of 5 microgram/hour buprenorphine 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.

[Nationally completed name] should not be used at higher doses than recommended.

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

During the titration process, the dose may be adjusted every 3 days (72 hours). Thereafter, the 7-day dosing interval should be maintained. Subsequent dose increases may then be titrated based on the need for supplemental pain relief and the patient's analgesic response to the transdermal patch.

To increase the dose, a patch with a higher strength should replace the transdermal 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 transdermal patches are applied at the same time, up to a maximum total dose of 40 microgram/hour buprenorphine. Patients should be carefully and regularly monitored to assess the optimum dose and duration of treatment.

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

Duration of administration
[Nationally completed name] should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with [Nationally completed name] 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 transdermal 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 [Nationally completed name] 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 transdermal 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).

Special populations
Elderly patients
No dose adjustment of buprenorphine transdermal patches is required in elderly patients.

Renal impairment
No special dose adjustment of buprenorphine transdermal patches 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, such patients should be carefully monitored during treatment with buprenorphine transdermal patches.

There is no need for dose adjustment of [Nationally completed name] in patients with mild to moderate hepatic impairment.

Patients with severe hepatic impairment may accumulate buprenorphine during [Nationally completed name] treatment. Alternate therapy should be considered, and buprenorphine transdermal patches should be used with caution, if at all, in such patients.

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

Paediatric population
The safety and efficacy of buprenorphine transdermal patches in children and adolescents below 18 years of age has not been established. No data are available.

Method of administration
Transdermal use.

Treatment goals and discontinuation
Before initiating treatment with [Nationally completed name], a treatment strategy including treatment duration and treatment goals, and a plan for end of the treatment, should be agreed together with the patient, in accordance with pain management guidelines. During treatment, there should be frequent contact between the physician and the patient to evaluate the need for continued treatment, consider discontinuation and to adjust dosages if needed. When a patient no longer requires therapy with [Nationally completed name], it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered (see section 4.4).

Duration of treatment
[Nationally completed name] should not be used longer than necessary.

Transdermal patch to be worn for 7 days. The patch must not be divided or cut into pieces.

Transdermal patch application
In order to ensure effective analgesia of buprenorphine and to minimise the potential of skin reactions (see section 4.4), the following directions of use should be followed:
[Nationally completed name] 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.
[Nationally completed name] 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 transdermal patch is applied. The transdermal patches 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 transdermal 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 transdermal patch. If a transdermal patch falls off, a new one should be applied and worn for 7 days.

A new transdermal patch should not be applied to the same skin site for the subsequent 3-4 weeks (see section 5.2).

While wearing the patch, patients should be advised to avoid exposing the application site to external heat sources (see section 4.4).

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 transdermal patches should be used with particular caution in patients with:
- respiratory depression
- CNS depressants co-administration (see below and section 4.5)
- serotonergic agents (see below and section 4.5)
- psychological dependence (addiction), abuse profile and history of substance and/or alcohol abuse (see below)
- sleep apnoea
- acute alcohol intoxication
- head injury, intracranial lesions or increased intracranial pressure, shock, a reduced level of consciousness of uncertain origin
- severely impaired hepatic function (see section 4.2)
- constipation

Sleep-related breathing disorders
Opioids can cause sleep-related breathing disorders including central sleep apnoea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, decreasing the total opioid dose should be considered.

Respiratory depression
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 (see section 4.5). Caution should be exercised when prescribing [Nationally completed name] to patients known to have, or suspected of having, problems with drug or alcohol abuse or serious mental illness.

Buprenorphine is a μ-opioid partial agonist, acting as a full agonist with respect to analgesia and as a partial agonist with respect to its respiratory depressant properties (see section 5.1).

Risk from concomitant use of sedative medicinal products such as benzodiazepines or related medicinal products
Concomitant use of buprenorphine and sedative medicinal products such as benzodiazepines or related medicinal products may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedative medicinal products should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe buprenorphine concomitantly with sedative medicinal products, 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 buprenorphine and other serotonergic agents, such as selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).
If concomitant treatment with other serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.
Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.
If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

Long-term treatment effects and tolerance
In all patients, tolerance to the analgesic effects, hyperalgesia, physical dependence, and psychological dependence may develop upon repeated administration of opioids, whereas incomplete tolerance is developed for some side effects like opioid induced constipation. Particularly in patients with chronic non-cancer pain, it has been reported that they may not experience a meaningful amelioration in pain intensity from continuous opioid treatment in the long term. It is recommended to re-evaluate the appropriateness of continued use of buprenorphine transdermal patches regularly at the time of prescription renewals in patients. When it is decided that there is no benefit for continuation, gradual down titration should be applied to address withdrawal symptoms.

Opioid use disorder (abuse and dependence)
Repeated use of buprenorphine transdermal patches can lead to Opioid use disorder (OUD). A higher dose and longer duration of opioid treatment can increase the risk of developing OUD. Abuse or intentional misuse of buprenorphine transdermal patches 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 buprenorphine 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 treated with opioids should be monitored for signs of OUD, such as drugseeking behaviour (e.g. too early requests for refills), particularly with patients at increased risk. This includes the review of concomitant opioids and psycho-active medicinal products (like benzodiazepines). For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered. If opioid discontinuation is to occur see section 4.4 “Long-term treatment effects and tolerance”.

In humans limited euphorigenic effects have been observed with buprenorphine. This may result in some abuse of the product.

Withdrawal syndrome
A withdrawal syndrome may occur upon abrupt cessation of therapy. 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. When a patient no longer requires therapy with buprenorphine, it may be advisable to taper the dose gradually to prevent symptoms of withdrawal. Administration of buprenorphine to persons who are physically dependent on full μ-opioid agonists may precipitate an abstinence syndrome depending on the level of physical dependence, and the timing and dose of buprenorphine.

Skin reactions at application site
To minimise the risk of occurrence of application site skin reactions, it is important to follow the posology instructions (see section 4.2).

Application site reactions with buprenorphine transdermal patches are usually presented by a mild or moderate skin inflammation (contact dermatitis), and their typical appearance may include erythema, oedema, pruritus, rash, small blisters (vesicles), and painful/burning sensation at the application site. Most commonly the cause is skin irritation (irritant contact dermatitis), and these reactions resolve spontaneously after the removal of the buprenorphine transdermal patches.

Patients and caregivers should be instructed accordingly to monitor the application sites for such reactions. If allergic contact dermatitis is suspected, relevant diagnostic procedures should be performed to determine if sensitisation has occurred and its actual cause (buprenorphine and/or other ingredients of the patch).

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

Buprenorphine transdermal patches are 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.

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

Endocrine system
Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone. Clinical symptoms may be manifest from these hormonal changes.

Patients with fever or exposed to external heat

While wearing the transdermal patch, patients should be advised to avoid exposing the application site to external heat sources, such as heating pads, electric blankets, hot water bottles, heat lamps, sauna, hot tubs, and heated water beds, etc., as an increase in absorption of buprenorphine may occur. Severe febrile illness may also increase the rate of buprenorphine absorption from buprenorphine transdermal patches resulting in increased plasma concentrations of buprenorphine and thereby increased risk of opioid reactions.

Athletes must be aware that this medicinal product may cause a positive reaction to sports doping control tests. Use of [nationally completed name] as a doping agent may become a health hazard.

4.5 Interaction with other medicinal products and other forms of interaction

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 use of buprenorphine transdermal patches with ketoconazole as compared to buprenorphine transdermal patches alone.

The interaction between buprenorphine and CYP3A4 enzyme inducers has not been studied. Co-administration of buprenorphine transdermal patches 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 transdermal patches must not be used concomitantly with MAOIs or in patients who have received MAOIs within the previous two weeks (see section 4.3).

[Nationally completed name] should be used cautiously when co-administered with:
- Sedative medicinal products such as benzodiazepines or related medicinal products:
  The concomitant use of opioids with sedative medicinal products such as benzodiazepines or related medicinal products 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).
- 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, antipsychotics, clonidine and related substances. These combinations increase the CNS depressant activity. The concomitant use of buprenorphine with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death (see section 4.4).
- Serotonergic medicinal products, such as selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).
- Anticholinergics or medications with anticholinergic activity (e.g. tricyclic antidepressants, antihistamines, antipsychotics, muscle relaxants, anti-Parkinson drugs) may result in increased anticholinergic adverse effects.

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

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amounts of data from the use of buprenorphine transdermal patches in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Buprenorphine crosses the placenta and buprenorphine and the active metabolite norbuprenorphine can be detected in newborn serum, urine and meconium following in utero exposure.
Towards the end of pregnancy high doses of buprenorphine may induce respiratory depression in the newborn infant even after a short period of administration. Prolonged use of buprenorphine during pregnancy can result in neonatal opioid withdrawal syndrome.
Therefore, [Nationally completed name] should not be used during pregnancy and in women of childbearing potential who are not using effective contraception unless the potential benefit justifies the potential risk to the foetus.

Breast-feeding
Buprenorphine is excreted in human milk. Studies in rats have shown that buprenorphine may inhibit lactation. Available pharmacodynamic/toxicological data in animals have shown excretion of buprenorphine in milk (see section 5.3). A risk to the newborn/infants cannot be excluded. [Nationally completed name] should be used with caution during breast-feeding.

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 transdermal patches have a major influence on the ability to drive and use machines. Even when used according to instructions, buprenorphine transdermal patches 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 adverse reactions (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 transdermal patch has been removed.

4.8 Undesirable effects

Serious adverse reactions that may be associated with buprenorphine transdermal patches 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 (≥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)

System organ class	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Immune system disorders			Hypersensitivity	Anaphylactic reaction		Anaphylactoid reaction
Metabolism and nutrition disorders		Anorexia		Dehydration		
Psychiatric disorders		Confusion, depression, insomnia, nervousness, anxiety	Affect lability, sleep disorder, restlessness, agitation, euphoric mood, hallucinations, libido decreased, nightmares, aggression	Psychotic disorder	Drug dependence (see section 4.4), mood swings	Depersona-lisation
Nervous system disorders	Headache, dizziness, somnolence	Tremor	Sedation, dysgeusia, dysarthria, hypoaesthesia, memory impairment, migraine, syncope, abnormal coordination, disturbance in attention, paraesthesia	Balance disorder, speech disorder	Involuntary muscle contractions	Seizures, sleep apnoea syndrome, hyperalgesia
Eye disorders			Dry eye, blurred vision	Visual disturbance, eyelid oedema, miosis		

System organ class	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
Ear and labyrinth disorders			Tinnitus, vertigo		Ear pain	
Cardiac disorders			Palpitations, tachycardia	Angina pectoris		
Vascular disorders			Hypotension, circulatory collapse, hypertension, flushing	Vasodila-tation, orthostatic hypotension		
Respiratory, thoracic and mediastinal disorders		Dyspnoea	Cough, wheezing, hiccups	Respiratory depression, respiratory failure, asthma aggravated, hyperventi-lation, 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	Face oedema	Pustules, vesicles	Dermatitis contact, application site skin discoloration
Musculoskeletal and connective tissue disorders		Muscular weakness	Myalgia, muscle spasms			
Renal and urinary disorders			Urinary incontinence, urinary retention, urinary hesitation			
Reproductive system and breast disorders				Erectile dysfunction, sexual dysfunction		

System organ class	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
General disorders and administration site conditions	Application site reaction including erythema, oedema, pruritus, rash	Tiredness, asthenia, peripheral oedema,	Fatigue, pyrexia, rigors, oedema, drug withdrawal syndrome, application site dermatitis*, chest pain	Influenza like illness		Drug withdrawal syndrome neonatal, drug tolerance
Investigations			Alanine aminotransferase increased, Weight decreased			
Injury, poisoning and procedural complications			Accidental injury, fall			

[1]Includes common signs and symptoms of contact dermatitis (irritative or allergic): erythema, oedema, pruritus, rash, vesicles, painful/burning sensation at the application site.

* In some cases delayed local allergic reactions (allergic contact dermatitis) occurred with marked signs of inflammation. Mechanical injuries during patch removal (e.g. laceration) are also possible in patients with fragile skin. Chronic inflammation may lead to long-lasting sequelae, such as post inflammatory hyper- and hypopigmentation, as well as dry and thick scaly skin lesions, which may closely resemble scars. In such cases treatment with [Nationally completed name] should be terminated (see sections 4.3 and 4.4).

Drug dependence
Repeated use of buprenorphine can lead to drug dependence, even at therapeutic doses. The risk of drug dependence may vary depending on a patient's individual risk factors, dosage, and duration of opioid treatment (see section 4.4).

[Nationally completed name] has a low risk of physical dependence. After discontinuation of buprenorphine transdermal patches, 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 transdermal patches, 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 national reporting system listed in Appendix V.

4.9 Overdose

Symptoms
Symptoms similar to those of other centrally acting analgesics are to be expected. These may include respiratory depression, including apnoea, sedation, drowsiness, nausea, vomiting, cardiovascular collapse and marked miosis.

Treatment
Any transdermal patches should be removed from the patient's skin. A patent airway should be established and maintained, respiration 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 mu-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

Mechanism of action
Buprenorphine is a μ-opioid agonist, acting as a full agonist with respect to analgesia and as a partial agonist with respect to its respiratory depressant properties. It also has antagonistic activity at the kappa opioid receptor.

Other pharmacologic effects: In vitro and animal studies indicate various effects of natural opioids, such as morphine, on components of the immune system; the clinical significance of these findings is unknown. Whether buprenorphine, a semisynthetic opioid, has immunological effects similar to morphine is unknown.

Clinical efficacy and safety
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 osteoarthritis (OA) and back pain. Buprenorphine transdermal patches 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 microgram/hour strength, 35% on the 10 microgram/hour strength and 48% on the 20 microgram/hour strength.

Buprenorphine has a potential risk of respiratory depression. However, evidence suggests that buprenorphine is a partial agonist with respect to its respiratory depressant activity and a ceiling effect has been reported following intravenous doses of greater than 2 micrograms/kg. Respiratory

depression appears to be a rare occurrence at therapeutic doses of the transdermal preparation (up to 40 micrograms/hour).

5.2 Pharmacokinetic properties

Each transdermal patch provides a steady delivery of buprenorphine for up to seven days. Steady state is achieved during the second application period. After removal of [Nationally completed name], buprenorphine concentrations decline with mean elimination half lifes ranging from 31 to 45 hours.

Absorption
Following [Nationally completed name] application, buprenorphine diffuses from the transdermal patch through the skin. In clinical pharmacology studies, the median time for buprenorphine transdermal patches 10 microgram/hour to deliver detectable buprenorphine concentrations (25 picograms/ml) was approximately 17 hours. Analysis of residual buprenorphine in transdermal patches after 7-day use shows approximately 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 transdermal patch 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 transdermal patch 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 transdermal 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 transdermal patch is not recommended (see section 4.4). A heating pad applied to a buprenorphine transdermal patch site immediately after patch removal did not alter absorption from the skin depot.

Distribution
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.

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 application of buprenorphine transdermal patches 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 55 l/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 20 microgram/hour transdermal patch. The effect on metabolism catalysed by CYP2C8, CYP2C9 and CYP2C19 has not been studied.

5.3 Preclinical safety data

Reproductive and developmental 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.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Release liner (to be removed before applying the patch):
Poly(ethylene terephthalate) foil, siliconized

Adhesive matrix (containing buprenorphine):

Levulinic acid
Oleyl oleate
Povidone K90
Poly[acrylic acid-co-butylacrylate-co-(2-ethylhexyl)acrylate-co-vinylacetate] (5:15:75:5)

Separating film (between the adhesive matrices with and without buprenorphine):
Poly(ethylene terephthalate) foil

Cover patch:
Acrylate adhesive
Polyurethane backing foil
Printing ink

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

Each transdermal patch is individually packed in a child resistant sachet made of PET/Alu/PE.

Carton containing 4, 8 or 12 transdermal patches.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Used transdermal patches should be folded with the adhesive surface inwards. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

Sandoz B.V.
Hospitaaldreef 29
1315 RC Almere
Nederland

8. NUMMER(S) VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

RVG 128363, Buprenorfine Sandoz 25 microgram/uur 7 dagen, pleister voor transdermaal gebruik
RVG 128364, Buprenorfine Sandoz 30 microgram/uur 7 dagen, pleister voor transdermaal gebruik
RVG 128366, Buprenorfine Sandoz 40 microgram/uur 7 dagen, pleister voor transdermaal gebruik

9. DATUM VAN EERSTE VERLENING VAN DE VERGUNNING/VERLENGING VAN DE VERGUNNING

Datum van eerste verlening van de vergunning: 3 juni 2022

10. DATUM VAN HERZIENING VAN DE TEKST

Laatste gedeeltelijke wijziging betreft de rubrieken 4.2, 4.4, 4.5 en 4.8: 19 december 2024