SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

{[Nationally completed name] 5 microgram/hour transdermal patch}
{[Nationally completed name] 10 microgram/hour transdermal patch}
{[Nationally completed name] 15 microgram/hour transdermal patch}
{[Nationally completed name] 20 microgram/hour transdermal patch}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

{[Nationally completed name] 5 microgram/hour transdermal patch}:
Each transdermal patch contains 5 mg of buprenorphine per 6.25 cm^2, releasing 5 micrograms of buprenorphine per hour.
{[Nationally completed name] 10 microgram/hour transdermal patch}:
Each transdermal patch contains 10 mg of buprenorphine per 12.5 cm^2, releasing 10 micrograms of buprenorphine per hour.
{[Nationally completed name] 15 microgram/hour transdermal patch}:
Each transdermal patch contains 15 mg of buprenorphine per 18.75 cm^2, releasing 15 micrograms of buprenorphine per hour.
{[Nationally completed name] 20 microgram/hour transdermal patch}:
Each transdermal patch contains 20 mg of buprenorphine per 25 cm^2, releasing 20 micrograms of buprenorphine per hour.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Transdermal patch.

The product is composed of a drug containing transdermal patch 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 5 µg/h’
‘Buprenorphinum 10 µg/h’
‘Buprenorphinum 15 µg/h’
‘Buprenorphinum 20 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

Patients aged 18 years and over

The lowest [Nationally completed name] strength ([Nationally completed name] 5 microgram/hour transdermal patch) should be used as the initial dose. Consideration should be given to the previous opioid history of the patient (see section 4.5) as well as to the current general condition and medical status of the patient.

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

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

Titration

During initiation and titration with [Nationally completed name], patients should use the usual recommended doses of short-acting supplemental analgesics (see section 4.5) as needed until analgesic efficacy with [Nationally completed name] is attained.

The dose should not be increased before 3 days, when the maximum effect of a given dose is established. Subsequent dose increases may then be titrated based on the need for supplemental pain relief and the patient's analgesic response to the transdermal patch.

To increase the dose, a patch of 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. Patients should be carefully and regularly monitored to assess the optimum dose and duration of treatment.

Conversion from opioids

[Nationally completed name] can be used as an alternative to treatment with other opioids. Such patients should be started on the lowest available strength ([Nationally completed name] 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 [Nationally completed name] is required in elderly patients.

Renal impairment

No special dose adjustment of [Nationally completed name] 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 [Nationally completed name].
Patients with severe hepatic impairment may accumulate buprenorphine during [Nationally completed name] treatment. Alternate therapy should be considered, and [Nationally completed name] should be used with caution, if at all, in such patients.

Paediatric population

As [Nationally completed name] has not been studied in patients under 18 years of age the use of [Nationally completed name] in patients below this age is not recommended.

Method of administration

Transdermal use.

Transdermal patch application:
[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. [Nationally completed name] 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.

Bathing, showering, or swimming should not affect the transdermal patch. If a patch falls off, a new one should be applied.

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

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- in 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

[Nationally completed name] should be used with particular caution in patients with acute alcohol intoxication, 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 (see section 4.5).

<u>Risk from concomitant use of sedative medicinal products such as benzodiazepines or related medicinal products</u>
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).

[Nationally completed name] is not recommended for analgesia in the immediate post-operative period or in other situations characterized 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.

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 transdermal 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.

Athletes must be aware that this medicinal product may cause a positive reaction to sports doping control tests.

4.5 Interaction with other medicinal products and other forms of interaction

[Nationally completed name] 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 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 [Nationally completed name] 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
[Nationally completed name] should be used cautiously 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, neuroleptics, clonidine and related substances. These combinations increase the CNS depressant activity.

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 [Nationally completed name] 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 newborn infant 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 newborn infant. Therefore, [Nationally completed name] should not be used during pregnancy and in women of childbearing potential who are not using effective contraception.

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). Therefore, the use of [Nationally completed name] during lactation should be avoided.

Fertility
No human data on the effect of buprenorphine on fertility are available. In a fertility and early embryonic development study, no effects on reproductive parameters were observed in male or female rats (see section 5.3).

4.7 Effects on ability to drive and use machines

[Nationally completed name] has a major influence on the ability to drive and use machines.
Even when used according to instructions, [Nationally completed name] 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.

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 transdermal patch has been removed.

4.8 Undesirable effects

Serious adverse reactions that may be associated with [Nationally completed name] 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
Immune system disorders			hypersensitivity		anaphylactic reaction, anaphylactoid reaction
Metabolism and nutrition disorders		anorexia	dehydration		
Psychiatric disorders		confusion, depression, insomnia, nervousness	sleep disorder, restlessness, agitation, depersonalisation, euphoric mood, affect lability, anxiety, hallucinations, nightmares	psychotic disorder, decreased libido	drug dependence, mood swings
Nervous system disorders	headache, dizziness, somnolence	paraesthesia	sedation, dysgeusia, dysarthria, hypoaesthesia, memory impairment, migraine, syncope, tremor, abnormal coordination, disturbance in attention	balance disorder, speech disorder	involuntary muscle contractions

System organ class	Very common	Common	Uncommon	Rare	Very rare
Eye disorders			dry eye, blurred vision	visual disturbance, eyelid oedema, miosis	
Ear and labyrinth disorders			tinnitus, vertigo		ear pain
Cardiac disorders			angina pectoris, palpitations, tachycardia		
Vascular disorders		vasodilatation	hypotension, circulatory collapse, hypertension, flushing		
Respiratory, thoracic and mediastinal disorders		dyspnoea	asthma aggravated, cough, hypoxia, rhinitis, wheezing, hyperventilation, hiccups	respiratory depression, respiratory failure	
Gastrointestinal disorders	constipation, dry mouth, nausea, vomiting	abdominal pain, diarrhoea, dyspepsia	flatulence	diverticulitis, dysphagia, ileus	
Hepatobiliary disorders				biliary colic	
Skin and subcutaneous tissue disorders	pruritus, erythema	rash, sweating, exanthema	dry skin, face oedema, urticaria, dermatitis contact		pustules, vesicles

System organ class	Very common	Common	Uncommon	Rare	Very rare
Musculoskeletal and connective tissue disorders			muscle cramp, myalgia, muscular weakness, muscle spasms		
Renal and urinary disorders			urinary retention, micturition disorder		
Reproductive system and breast disorders				erectile dysfunction, sexual dysfunction	
General disorders and administration site conditions	application site pruritus, application site reaction	tiredness, asthenia, pain, peripheral oedema, application site erythema, application site rash, chest pain	fatigue, influenza like illness, pyrexia, rigors, malaise, oedema, drug withdrawal syndrome	application site inflammation*	
Investigations			alanine aminotransferase increased, weight decreased		
Injury, poisoning and procedural complications			accidental injury, fall		

* In some cases delayed local allergic reactions occurred with marked signs of inflammation. In such cases treatment with [Nationally completed name] should be terminated.

Buprenorphine has a low risk of physical dependence. After discontinuation of [Nationally completed name], 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 [Nationally completed name], 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 include respiratory depression, 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 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. 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, oripavine derivatives
ATC code: N02AE01

Mechanism of action
Buprenorphine is a partial agonist opioid, acting at the mu opioid receptor. It also has antagonistic activity at the kappa opioid receptor.

Clinical efficacy and safety
Efficacy has been demonstrated in five pivotal phase III studies of up to 12 weeks duration in patients with nonmalignant pain of various aetiologies. These included patients with moderate and severe 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.

5.2 Pharmacokinetic properties

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 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. A heating pad applied to a buprenorphine transdermal patch site immediately after transdermal 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 bloodbrain and placental barriers. Concentrations in the brain (which contained only unchanged buprenorphine) after parenteral administration were 2-3 times higher than after oral administration. After intramuscular or oral administration buprenorphine apparently accumulates in the foetal gastrointestinal lumen – presumably due to biliary excretion, as enterohepatic circulation has not fully developed.

Each transdermal patch provides a steady delivery of buprenorphine for up to seven days. Steady state is achieved during the first application. After removal of [Nationally completed name], buprenorphine concentrations decline, decreasing approximately 50% in 12 hours (range 10–24 h).

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 [Nationally completed name] 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 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 [Nationally completed name] 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

Adhesive matrix (without buprenorphine):
Acrylate adhesive

Backing layer (printed):
Polyurethane backing foil
Printing ink

6.2 Incompatibilities

Not applicable

6.3 Shelf life

[DE/H/4045-4046/001]
18 months

[DE/H/4045-4046/002-003-004]
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.

[DE/H/4045/001-002-003-004]: Carton containing 1, 2, 3, 4, 5, 8, 10, 12 or 20 transdermal patches.
[DE/H/4046/001-002-003-004]: Carton containing 2, 4, 5, 8, 10, 12 or 20 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 in wards. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]