Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Transtec 52.5 micrograms/h Transdermal Patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One transdermal patch contains 30 mg buprenorphine.

Area containing the active substance: 37.5 cm^2
Nominal release rate: 52.5 micrograms of buprenorphine per hour (over a period of 96 hours).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch.
Skin coloured transdermal patch with rounded corners marked:
Transtec 52.5 µg/h, buprenorphinum 30 mg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Transtec is not suitable for the treatment of acute pain.

4.2 Posology and method of administration

Posology
Patients over 18 years of age
Treatment goals and discontinuation
Before initiating treatment with TRANSTEC®, 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 TRANSTEC®, 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) .

The lowest possible dosage providing adequate pain relief should be given. Three transdermal patch strengths are available to provide such adaptive treatment: Transtec® 35 micrograms/h, Transtec® 52.5 micrograms/h and Transtec® 70 micrograms/h.
Initial dose selection: patients who have previously not received any analgesics should start with the lowest transdermal patch strength (Transtec® 35 micrograms/h). Patients previously given a WHO step-I analgesic (non-opioid) or a step-II analgesic (weak opioid) should also begin with Transtec® 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 Transtec® 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 (Transtec® 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 Transtec® must be adapted to the requirements of the individual patient and checked at regular intervals.
After application of the first Transtec® 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 Transtec® and appropriate rescue medication on demand in the following 12 hours.
Dose titration and maintenance therapy
Transtec® should be replaced after 96 hours (4 days) at the latest. For convenience of use, the transdermal patch can be changed twice a week at regular intervals, e.g. always on Monday morning and Thursday evening. 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 Transtec® 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.
Supplementary administration of fast acting strong analgesics for treatment of breakthrough pain may be necessary, not only during dose titration but also during maintenance therapy.
If additional analgesic doses are regularly required, a switch to the next higher buprenorphine patch strength can be considered.
Special population
Paediatric population
As Transtec® 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 Transtec® 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 Transtec®.
Method of application
Transtec® 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 Transtec® should be avoided.
The skin must be completely dry before application. Transtec® is to be applied immediately after removal from the sachet. Following removal of the release liner, 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).
Transtec® should be worn continuously for up to 4 days. After removal of the previous transdermal patch a new Transtec® 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.
Duration of administration
Transtec® should not be used longer than necessary. If long-term pain treatment with Transtec® 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 Transtec®
After removal of Transtec® 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 Transtec® is to be followed by other opioids. As a general rule, a subsequent opioid should not be administered within 24 hours after removal of Transtec®. For the time being onlylimited information is available on the starting dose of other opioids administered after discontinuation of Transtec®.

4.3 Contraindications

Transtec® is contraindicated in:

- 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
- pregnancy (see section 4.6)

4.4 Special warnings and precautions for use

Transtec® 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.
In healthy volunteer and patient studies with Transtec®, withdrawal reactions have not been observed. However, after long-term use of Transtec® withdrawal symptoms, similar to those occurring during opiate withdrawal, cannot be entirely excluded (see section 4.8). These symptoms are: agitation, anxiety, nervousness, insomnia, hyperkinesia, tremor and gastrointestinal disorders.
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.
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 TRANSTEC®. Repeated use of TRANSTEC® 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 TRANSTEC® 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 (eg. major depression, anxiety and personality disorders).
Before initiating treatment with TRANSTEC® 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 behaviour (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.
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 Transtec® treatment.
Athletes should be aware that this medicine may cause a positive reaction to sports doping control tests.
Risk from concomitant use of sedating medicinal products such as benzodiazepines or related substances
Concomitant use of Transtec® and sedating medicinal products such as benzodiazepines or related substances may result in sedation, respiratory depression, coma and death. Because of these risks, concomitant prescribing with these sedating medicinal products should be reserved for patients for whom alternative treatment options are not possible. If a decision is made to prescribe Transtec® concomitantly with sedating medicinal products, the lowest effective dose of Transtec® should be used, and the duration of the concomitant 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).
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, consider decreasing the total opioid dosage.
Serotonin syndrome
Concomitant administration of Transtec® 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.
Paediatric population
As Transtec® 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 treatment. Therefore on treatment with Transtec®, attention should be paid to the increased possibility of opioid reactions in febrile patients or those with increased skin temperature due to other causes.

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 Transtec® cannot be ruled out (see section 4.3).

When Transtec® 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.The concomitant use of Transtec® with gabapentinoids (gabapentin and pregabalin) may result in respiratory depression, hypotension, profound sedation, coma or death (see section 4.4)'. This applies also to alcohol.
Transtec® should be used cautiously when co-administered with:

- 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).
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Administered together with inhibitors or inducers of CYP 3A4 the efficacy of Transtec® may be intensified (inhibitors) or weakened (inducers).
Sedating medicinal products such as benzodiazepines or related substances
The concomitant use of opioids with sedating medicinal products such as benzodiazepines or related substances increases the risk of sedation, respiratory depression, coma and death because of an additive CNS depressant effect. The dose of Transtec® and the duration of the concomitant use should be limited (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 Transtec® 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 Transtec® is contraindicated during pregnancy.
Breast-feeding
Buprenorphine is excreted in human milk. In rats, buprenorphine has been found to inhibit lactation.
Transtec® should not be used during lactation.
Fertility
The effect of buprenorphine on human fertility is unknown. Buprenorphine did not affect fertility in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Transtec has major influence on the ability to drive and use machines.
Even when used according to instructions, Transtec 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 Transtec is used in conjunction with other centrally acting substances including alcohol, tranquillisers, 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 Transtec and 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.

4.8 Undesirable effects

The following adverse reactions were reported after administration of Transtec® in clinical studies and from postmarketing 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.
The most commonly reported local adverse reactions were erythema and pruritus.

b) **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, disequilibrium, 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
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
Not known: dermatitis contact, application skin discolouration
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 Transtec® should be terminated.

Drug dependence
Repeated use of Transtec® 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).

After discontinuation of Transtec®, 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 Transtec® 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.
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

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 Transtec® 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 principle, 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. Coma, respiratory arrest and death may also occur following an opioid overdose.
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 described in literature as follows:
o Morphine p.o. : BUP i.m. as 1 : 67 - 150 (single dose; acute pain model)
o Morphine p.o. : BUP s.l. as 1 : 60 - 100 (single dose, acute pain model; multiple dose , chronic pain, cancer pain)
o 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 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.

b) Characteristics of Transtec in healthy volunteers
After the application of Transtec buprenorphine is absorbed through the skin. The continuous delivery of buprenorphine into the systemic circulation is by controlled release from the adhesive polymer-based matrix system.

After the initial application of Transtec the plasma concentrations of buprenorphine gradually increase, and after 12-24 h the plasma concentrations reach the minimum effective concentration of 100 pg/ml. From the studies performed with the Transtec 35 micrograms/h in healthy volunteers, an average C_{max} of 200 to 300 pg/ml and an average t_{max} of 60-80 h were determined. In one volunteer study, Transtec 35 micrograms/h and Transtec 70 micrograms/h were applied in a cross-over design. From this study, dose proportionality for the different strengths was demonstrated.

After removal of Transtec the plasma concentrations of buprenorphine steadily decrease and are eliminated with a half-life of approx. 30 hours (range 22 - 36). Due to the continuous absorption of buprenorphine from the depot in the skin elimination is slower 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 post-implantation loss, although only at maternal toxic doses.
Studies in rats showed diminished intra-uterine growth, delays in the development of certain neurological functions and high peri/post-natal 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

Adhesive matrix (containing buprenorphine): [(Z)-octadec-9-en-1-yl] oleate, povidone K90, 4-oxopentanic acid, poly[acrylic acid-co-butylacrylate-co-(2-ethylhexyl)acrylate-co-vinylacetate] (5:15:75:5), cross-linked

Adhesive matrix (without buprenorphine): poly[acrylic acid-co-butylacrylate-co-(2-ethylhexyl)acrylate-co-vinylacetate] (5:15:75:5), not cross-linked

Separating foil between the adhesive matrices with and without buprenorphine: poly(ethyleneterephthalate) – foil

Backing layer: poly(ethyleneterephthalate) – tissue

Release liner (on the front covering the adhesive matrix containing buprenorphine): poly(ethyleneterephthalate) – foil, siliconised, coated on one side with aluminium

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Type of container:
Sealed child-resistant sachet, composed of identical top and bottom layers of heat-sealable laminate, comprising (from outside to inside) paper, polyethylene terephthalate, polyethylene, aluminium and poly(acrylic acid-co-ethylene) (= surlyn).

Pack sizes:
Packs containing 3, 4, 5, 6, 8, 10, 11, 12, 16, 18, 20 or 24 individually sealed transdermal 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

Grünenthal GmbH
Zieglerstrasse 6
Aachen
North Rhine-Westphalia
52078
Germany

8 MARKETING AUTHORISATION NUMBER

PA1032/001/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd May 2002
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10 DATE OF REVISION OF THE TEXT

October 2025