Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Citanest Plain Dental, Prilocaine Hydrochloride 4% w/v Solution for Injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains Prilocaine Hydrochloride 40mg, (88mg per 2.2ml cartridge).

For list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection.
2.2ml glass cartridge containing a sterile clear aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Citanest Plain Dental is a local anaesthetic for use in dental infiltration anaesthesia and dental nerve block techniques.

4.2 Posology and method of administration

- Injections should always be made slowly with careful aspiration before and intermittently during injection to avoid inadvertent intravascular injection, which may have toxic effects.

- The lowest dose that results in effective anaesthesia should be used. The dose will also depend on the area of oral cavity to be anaesthetised, the vascularity of the oral tissues and technique of anaesthesia. The total dose must be adjusted to the age, size and physical status of the patient.

- For effective local anaesthesia in most dental procedures, an adequate dose of Citanest Plain Dental solution injected into the tissue is:

In normally healthy adults: 1-2 ml (=40-80 mg prilocaine hydrochloride).

Children under 10 years of age: ~1 ml (=~ 40 mg prilocaine hydrochloride).

- Due to the specific need for bone penetration, dental local anaesthetics contain high concentrations of the active agent (e.g. 40 mg/ml for Citanest Plain Dental). A combination of a high pressure induced by the use of a dental cartridge system and a rapid rate of injection may lead to complications (*see section 4.9. Overdose*) even after the injection of small amounts of local anaesthetic due to high concentration, especially following accidental intravascular injection, when the injected drug could travel in a retrograde manner along the vessel and, in cases of intra-arterial injection in the head and neck area, reach the brain without the same degree of dilution that occurs with an intravenous injection. For routine dental procedures, the recommended dose is 1-2 ml and a dose of 10 ml (=400 mg prilocaine hydrochloride) Citanest Plain Dental should not be exceeded.

4.3 Contraindications

Known history of hypersensitivity to local anaesthetic agents of the amide type or to other components of the solution.

Congenital or idiopathic methaemoglobinaemia.

4.4 Special warnings and precautions for use

The safety and effectiveness of the local anaesthetic agent, prilocaine hydrochloride, depend on the proper dosage, the correct injection technique, adequate precautions and readiness for emergencies.

Before administration a local anaesthetic drug, make sure that resuscitative equipment, such as equipment required for oxygenation and assisted ventilation, and drugs for the treatment of toxic reactions are immediately available.

The patient should be advised to exert caution to avoid inadvertent trauma to the lips, tongue, cheek mucosa or soft palate when these structures are anaesthetised. The ingestion of food should therefore be postponed until normal function returns.

In the head and neck area the intravascular injection of even small doses of local anaesthetics may cause systemic adverse reactions similar to those seen after the inadvertent intravascular injection of larger doses in other areas.

Even, if the dose of Citanest Plain in dental practice is generally small, some patients may require special attention to reduce the risk of dangerous side effects:

- Patients with partial or complete heart block due to the fact that local anaesthetics may depress myocardial conduction.
- Patients with advanced liver disease or severe renal dysfunction.
- The elderly and patients in poor general condition.
- Patients with epilepsy and impaired respiratory function.

Local anaesthetics should be administered with caution to patients with severe or untreated hypertension, severe heart disease, severe anaemia or circulatory failure from whatever cause or any other pathological condition. Local anaesthetics should be avoided when there is inflammation in the region of the proposed injection.

Citanest 4% is in a single dose vial for use on one patient during one treatment only. The remaining contents should be discarded.

4.5 Interaction with other medicinal products and other forms of interaction

Prilocaine should be used with caution in patients receiving antiarrhythmic drugs, since the toxic effects are additive.

Drugs which may predispose to methaemoglobin formation, e.g. sulfonamides, antimalarials and certain nitric compounds, could potentiate this adverse effect of prilocaine.

4.6 Pregnancy and lactation

Although safe use of prilocaine during pregnancy has not been established with respect to possible adverse effects upon foetal development, it is reasonable to assume that Citanest Plain Dental has been administered to a large number of pregnant women and women of childbearing age. No specific disturbances to the reproductive process have so far been reported, e.g. increased incidence of malformations or other direct or indirect harmful effects on the foetus.

Methaemoglobinaemia in the neonate has been reported after the administration of prilocaine to the mother in doses exceeding 600 mg.

Prilocaine may enter the mother's milk, but in such small amounts that there is generally no risk of this affecting the neonate.

4.7 Effects on ability to drive and use machines

Depending on dosage, local anaesthetics may have a very mild effect on mental function and may temporarily impair locomotion and co-ordination.

4.8 Undesirable effects

Reactions to Citanest Plain are very rare in the doses used in dental procedures. If adverse reactions occur, they are similar in character to those observed with other local anaesthetics. Psychogenic reactions in anticipation of or during the dental procedure are, however, common and may mimic the symptoms of a generalized systemic reaction to local anaesthetics.

Allergic reactions

Allergic reactions (in the most severe instances anaphylactic shock) to local anaesthetics of the amide type are rare.

Neurological complications

The incidence of adverse neurological reactions (e.g. persistent neurological deficit) associated with the use of local anaesthetics is very low. Neurological reactions may be dependent upon the particular drug used, the route of administration and the physical status of the patients. Many of these effects may be linked to the injection techniques, with or without a contribution by the drug (*see section 4.4, Special warnings and precautions for use*). Neurological reactions following regional nerve blocks have included persistent paraesthesia and sensory disturbances.

Acute systemic toxicity

Prilocaine can cause acute toxic effects if high systemic levels occur due to accidental intravascular injection, fast absorption or overdosage. (*see section 5.1, Pharmacodynamic properties* and *section 4.9, Overdose*).

Methaemoglobaemia

Cyanosis due to the formation of methaemoglobin may occur after the administration of prilocaine. The repeated administration of prilocaine, even in relatively small doses, can lead to clinically overt methaemoglobinaemia.

The conversion of haemoglobin to methaemoglobin is caused by the prilocaine metabolite, orthotoluidine, which has a long half-life and tends to accumulate, and in turn, its conversion to 4- and 6-hydroxytoluidine. Methaemoglobin have risen to clinically significant levels in patients receiving high doses of prilocaine. Cyanosis occurs when the methaemoglobin concentration in the blood reaches 1-2 g/100 ml (6-12% of the normal haemoglobin concentration).

Methaemoglobin oxidises only slowly back to haemoglobin, but this process can be greatly accelerated by giving methylene blue i.v. (*see section 4.9, Overdose*)

The reduction in the oxygen-carrying capacity in normal patients is marginal; hence the cyanosis is usually symptomless. However, in severely anaemic patients it may cause significant hypoxaemia. It is important to rule out other more serious causes of cyanosis such as acute hypoxaemia and and/or heart failure. In the dental dosage of prilocaine (1-2 ml Citanest Plain, i.e. 40-80 mg prilocaine hydrochloride), the occurrence of methaemoglobinaemia in dental practice appears remote. However, gross overdosage in dental practice has been reported to cause methaemoglobinaemia.

Note. Even low concentrations of methaemoglobin may interfere with pulse oximetry readings, including a false low oxygen saturation.

4.9 Overdose

Since prilocaine is the least toxic of the amino-amide local anaesthetics, it is particularly useful in situations when high dosage may be needed. This advantage, however, should be weighed against the risk of causing methaemoglobinaemia.

Acute emergencies are, in general, dose-related and may result from high plasma levels caused by excessive dosage, rapid absorption (i.e. rate of increase plasma concentration) or unintentional intravascular injection, or may result from hypersensitivity or diminished tolerance on the part of the patient.

Acute systemic toxicity

CNS reactions are excitatory or depressant and may be characterized by nervousness, tinnitus, twitching, euphoria, drowsiness, blurred or double vision, dizziness, convulsions, unconsciousness and possibly respiratory arrest. The excitatory reactions may be very brief or may not occur at all, in which case the first manifestation of toxicity is drowsiness merging into unconsciousness and even respiratory arrest.

Cardiovascular reactions are depressant and may be characterized by hypotension, myocardial depression, bradycardia and possibly cardiac arrest. Signs and symptoms of depression cardiovascular function may commonly result from a vasovagal reaction, particularly if the patient is in an upright position. Less commonly, they may occur as a direct effect of the drug. Failure to recognize premonitory signs such as sweating, a feeling of faintness, changes in pulse or sensorium may result in progressive cerebral hypoxia and seizure or serious cardiovascular collapse.

Cardiovascular effects are usually only seen in the most severe cases and are generally preceded by signs of toxicity in the central nervous system.

Acidosis or hypoxia in the patient may increase the risk and severity of toxic reactions. Such reactions involve the central nervous system and the cardiovascular system.

Treatment of acute toxicity

The immediate treatment of acute systemic toxicity is as follows:

a. Put the patient is a supine position. Raise the legs 30°-45° above the horizontal level.

b. Ensure a patent airway. If ventilation is inadequate, ventilate the patient, with oxygen if available. This is important since toxicity increases with acidosis.

c. The treatment of convulsions consists in ensuring a patent airway and arresting convulsions. Should convulsions persist despite adequate ventilation, 5-15 mg diazepam or 50-200 mg thiopentone sodium should be administered intravenously (to arrest the convulsions). Since this treatment may also depress respiration, the means of mechanically supporting or controlling ventilation should be available.

d. Supportive treatment of circulatory depression may require the administration of intravenous fluids and, when appropriate, a vasopressor (e.g. ephedrine 5-10 mg i.v. and repeated, if necessary, after 2-3 min) as governed by the clinical situation.

e. If the patient is unresponsive and the carotid pulse rate is totally absent, indicating cardiac arrest, effective cardiopulmonary resuscitation.

Treatment of acute methaemoglobinaemia

If clinical methaemoglobinaemia occurs, it can be rapidly treated by a single intravenous injection of a 1% methylene blue solution, 1 mg/kg body weight, over a 5 minute period. Cyanosis will disappear in about 15 minutes. This dose should not be repeated as methylene blue in high concentrations acts as a haemoglobin oxidant.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

*Pharmacotherapeutic group***:** Anaesthetics, local amides**.**
*ATC code***:** NO1BB04**.**

Prilocaine, like other local anaesthetics, causes a reversible blockade of impulse propagation along nerve fibres by preventing the inward movement of sodium ions through the nerve membrane. Local anaesthetics of the amide type are thought to act within the sodium channels of the nerve membrane.

Local anaesthetic drugs may also have similar effects on excitable membranes in the brain and myocardium. If excessive amounts of drug reach the systemic circulation rapidly (*see section 4.2, Posology and method of administration*), symptoms and signs of toxicity will appear, emanating mainly from the central nervous and cardiovascular systems.

Central nervous system toxicity (*see section 4.9, Overdose*) usually precedes the cardiovascular effects as it occurs at lower plasma concentrations. Direct effects of local anaesthetics on the heart include slow conduction, negative inotropism and eventually cardiac arrest.

5.2 Pharmacokinetic properties

Prilocaine has a pKa of 7.9 and an N-heptane/pH 7.4 buffer partition coefficient of 0.9.

Prilocaine is between 40% and 55% protein bound in plasma, mainly to alpha 1-acid glycoprotein.

Prilocaine redistributes rapidly from the blood and it has a large apparent distribution volume of between 190 L and 260 L.

The terminal elimination half-life of prilocaine is 1.6 h.

Prilocaine readily passes the placenta and free plasma concentrations are similar in both foetus and mother. In the presence of fetal acidosis, they may be slightly higher in the foetus, due to ion trapping. Information concerning the elimination half-life of prilocaine in neonates is not available.

In the liver, prilocaine is primarily metabolised by amide hydrolysis to o-toluidine and N-propylamine. o-Toluidine is subsequently hydroxylated to 2-amino-3-hydroxytoluene and 2-amino-5-hydroxytoluene metabolites which are believed to be responsible for the occurrence of methaemoglobinaemia.

Only a small proportion of prilocaine (less that 5%) is excreted unchanged in the urine. *In vitro* and animal studies have shown metabolism of prilocaine by the lung and kidney tissues.

5.3 Preclinical safety data

There is no preclinical data of relevance to the prescriber, which is additional to that already included in other sections of the SmPC

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Sodium Hydroxide
Hydrochloric Acid
Water for Injections

6.2 Incompatibilities

None known.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25ºC.

6.5 Nature and contents of container

2.2ml colourless borosilicate glass (Ph. Eur. Type 1). Each carton contains 100 cartridges. Each cartridge contains a rubber plunger and has an aluminium and rubber combination cap.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Use on one patient during one treatment only. Discard unused contents.

7 MARKETING AUTHORISATION HOLDER

Dentsply Limited
Hamm Moor Lane
Addlestone
Weybridge
Surrey KT15 2SE
United Kingdom
Trading as Dentsply Pharmaceuticals

8 MARKETING AUTHORISATION NUMBER

PA 1045/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1980

Date of last renewal: 01 April 2005

10 DATE OF REVISION OF THE TEXT

May 2007