

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1032/002/001

Case No: 2065739

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Grunenthal GmbH

Zieglerstr. 6, D-52078 Aachen, Germany

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Centradol 35 micrograms/h Transdermal Patch

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **21/05/2009**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Centradol 35 micrograms/h Transdermal Patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One transdermal patch contains 20 mg buprenorphine.

Area containing the active substance: 25 cm²

Nominal release rate: 35 micrograms of buprenorphine per hour (over a period of 96 hours).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch

Skin coloured transdermal patch with rounded corners marked:

Centradol 35 µg/h, buprenorphinum 20 mg

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

Centradol is not suitable for the treatment of acute pain.

4.2 Posology and method of administration

Posology

Patients over 18 years of age

The Centradol dosage should be adapted to the condition of the individual patient (pain intensity, suffering, individual reaction). The lowest possible dosage providing adequate pain relief should be given. Three transdermal patch strengths are available to provide such adaptive treatment: Centradol 35 micrograms/h, Centradol 52.5 micrograms/h and Centradol 70 micrograms/h.

Initial dose selection: patients who have previously not received any analgesics should start with the lowest transdermal patch strength (Centradol 35 micrograms/h). Patients previously given a WHO step-I analgesic (non-opioid) or a step-II analgesic (weak opioid) should also begin with Centradol 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 Centradol 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 (Centradol 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 Centradol must be adapted to the requirements of the individual patient and checked at regular intervals.

After application of the first Centradol 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 Centradol and appropriate rescue medication on demand in the following 12 hours.

Dose titration and maintenance therapy

Centradol 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 Centradol strength the amount of total opioids administered in addition to the previous transdermal patch should be taken into consideration, i.e. the total amount of opioids required, and the dosage adjusted accordingly. Patients requiring a supplementary analgesic (e.g. for breakthrough pain) during maintenance therapy may take for example one to two 0.2 mg buprenorphine sublingual tablets every 24 hours in addition to the transdermal patch. If the regular addition of 0.4 – 0.6 mg sublingual buprenorphine is necessary, the next strength should be used.

Patients under 18 years of age

As Centradol 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 Centradol 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.

Bupre 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 Centradol.

Method of application

Centradol 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 Centradol should be avoided.

The skin must be completely dry before application Centradol 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).

Centradol should be worn continuously for up to 4 days. After removal of the previous transdermal patch a new Centradoltransdermal 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

Centradol should under no circumstances be administered for longer than absolutely necessary. If long-term pain treatment with Centradol 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 Centradol

After removal of Centradol 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 Centradol is to be followed by other opioids. As a general rule, a subsequent opioid should not be administered within 24 hours after removal of Centradol. For the time being only limited information is available on the starting dose of other opioids administered after discontinuation of Centradol.

4.3 Contraindications

Centradol is contraindicated in:

- hypersensitivity to the active substance buprenorphine or to any of the excipients (for the excipients, see 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.
- pregnancy (see section 4.6)

4.4 Special warnings and precautions for use

Centradol must only be used with particular caution in acute alcohol intoxication, convulsive disorders, in patients with head injury, shock, a reduced level of consciousness of uncertain origin, increased intracranial pressure without the possibility of ventilation.

Buprenorphine occasionally causes respiratory depression. Therefore care should be taken when treating patients with impaired respiratory function or patients receiving medicinal products which can cause respiratory depression.

Buprenorphine has a substantially lower dependence liability than pure opioid agonists. In healthy volunteer and patient studies with Centradol, withdrawal reactions have not been observed. However, after long-term use of Centradol 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.

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 Centradol treatment.

As Centradol 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 Centradol, 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 Centradol cannot be ruled out (see section 4.3).

When Centradol is applied together with other opioids, anaesthetics, hypnotics, sedatives, antidepressants, neuroleptics, and in general, medicinal products that depress respiration and the central nervous system, the CNS effects may be intensified. This applies also to alcohol.

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

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data from the use of Centradol 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 Centradol is contraindicated during pregnancy.

Lactation

Buprenorphine is excreted in human milk. In rats, buprenorphine has been found to inhibit lactation. Centradol should not be used during lactation.

4.7 Effects on ability to drive and use machines

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

Even when used according to instructions, Centradol 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 Centradol 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 Centradol 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 Centradol in clinical studies and from postmarketing surveillance.

The frequencies are given as follows:

Very common ($\geq 1/10$)

Common ($\geq 1/100$, $< 1/10$)

Uncommon ($\geq 1/1,000$, $< 1/100$)

Rare ($\geq 1/10,000$, $< 1/1,000$)

Very rare ($\leq 1/10,000$)

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, dysequilibrium, paraesthesia (e.g.
 pricking or burning skin
 sensation)
- Very rare: muscle fasciculation, parageusia

Eye disorders

- Rare: visual disturbance, blurring of vision, eyelid oedema
- Very rare: miosis

Ear and labyrinth disorders

- Very rare: ear pain

Cardiac/Vascular disorders

- Uncommon: circulatory disorders (such as hypotension or, rarely, even circulatory collapse)
- Rare: hot flushes

Respiratory, thoracic and mediastinal disorders

- Common: dyspnoea
- Rare: respiratory depression
- Very rare: hyperventilation, hiccups

Gastrointestinal disorders

Very common:	nausea
Common:	vomiting, constipation
Uncommon:	dry mouth
Rare:	pyrosis
Very rare:	retching

Skin and subcutaneous tissue disorders

Very common:	erythema, pruritus
Common:	exanthema, diaphoresis
Uncommon:	rash
Rare:	urticaria
Very rare:	pustules, vesicles

Renal and urinary disorders

Uncommon:	urinary retention, micturition disorders
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Reproductive system and breast disorders

Rare:	decreased erection
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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 Centradol should be terminated.

Buprenorphine has a low risk of dependence. After discontinuation of Centradol, 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 Centradol 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.

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 Centradol 70 micrograms/h transdermal patch is about six times less than after the intravenous administration of the therapeutic dose of 0.3 mg buprenorphine.

Symptoms

In principal, on overdose with buprenorphine, symptoms similar to those of other centrally acting analgesics (opioids) are to be expected. These are: respiratory depression, sedation, somnolence, nausea, vomiting, cardiovascular collapse, and marked miosis.

Treatment

General emergency measures apply. Keep the airway open (aspiration!), maintain respiration and circulation depending on the symptoms. Naloxone has a limited impact on the respiratory depressant effect of buprenorphine. High doses are needed given either as repeated boluses or infusion (for example starting with a bolus administration of 1-2 mg intravenously. Having attained an adequate antagonistic effect, administration by infusion is recommended to maintain constant naloxone plasma levels). Therefore, adequate ventilation should be established.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Opioids, Oripavine derivatives. ATC code: N02AE01.

Buprenorphine is a strong opioid with agonistic activity at the mu-opioid receptor and antagonistic activity at the kappa-opioid receptor. Buprenorphine appears to have the general characteristics of morphine, but has its own specific pharmacology and clinical attributes.

In addition, numerous factors, e.g. indication and clinical setting, route of administration and the interindividual variability, have an impact on analgesia and therefore have to be considered when comparing analgesics.

In daily clinical practice different opioids are ranked by a relative potency, although this is to be considered a simplification.

The relative potency of buprenorphine in different application forms and in different clinical settings has been described in literature as follows:

- Morphine p.o. : BUP i.m. as 1 : 67 - 150 (single dose; acute pain model)
- Morphine p.o. : BUP s.l. as 1 : 60 - 100 (single dose, acute pain model; multiple dose , chronic pain, cancer pain)
- Morphine p.o. : BUP TTS as 1 : 75 - 115 (multiple dose, chronic pain)

Abbreviations:

p.o = oral; i.m. = intramuscular; s.l. = sublingual; TTS = transdermal; BUP = buprenorphine

Adverse reactions are similar to those of other strong opioid analgesics. Buprenorphine appears to have a lower dependence liability than morphine.

5.2 Pharmacokinetic properties

a) General characteristics of the active substance

Buprenorphine has a plasma protein binding of about 96%.

Buprenorphine is metabolised in the liver to *N*-dealkylbuprenorphine (norbuprenorphine) and to glucuronide conjugated metabolites. $\frac{2}{3}$ of the active substance is eliminated unchanged in the faeces and $\frac{1}{3}$ 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 Centradol in healthy volunteers

After the application of Centradol 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 Centradol 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 Centradol 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, Centradol 35 micrograms/h and Centradol 70 micrograms/h were applied in a cross-over design. From this study, dose proportionality for the different strengths was demonstrated. After removal of Centradol 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 postimplantation loss.

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-oxopentanoic 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 sachet, composed of identical top and bottom layers of heat-sealable laminate, comprising (from outside to inside) paper, low density polyethylene, aluminium and poly (acrylic acid-co-ethylene) (= surlyn).

Pack sizes:

Packs containing 3, 5, 10 or 30 individually sealed transdermal patches.

Not all pack sizes may be marketed.

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

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

7 MARKETING AUTHORISATION HOLDER

Grünenthal GmbH,
Zieglerstrasse 6,
D-52078 Aachen,
Germany

8 MARKETING AUTHORISATION NUMBER

PA1032/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 03 May 2002

Date of last renewal: 24 July 2006

10 DATE OF REVISION OF THE TEXT

February 2009