**IRISH MEDICINES BOARD ACTS 1995 AND 2006**

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

**(S.I. No.540 of 2007)**

**PA0980/002/001**
Case No: 2065595

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

**Cambridge Healthcare Supplies Limited**

**14D Wendover Road**, **Rackheath Industrial Estate**, **Norwich, Norfolk NR13 6LH**, **United Kingdom**

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

**Xepin 5 %w/w Cream**

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 **10/03/2010**.

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

Xepin 5 %w/w Cream

## 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Doxepin hydrochloride 5% w/w.
Excipients: Also contains cetyl alcohol 8% w/w

For a full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Cream
Soft, white cream.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

For the relief of pruritus associated with eczema.

### 4.2 Posology and method of administration

Adults and children over 12 years

A thin film of Xepin should be applied three to four times daily, to the affected area only. Clinical experience has shown that drowsiness is significantly more common in patients applying cream to more than 10% of the body surface area, therefore, the maximum coverage should be less than 10% of body surface area. For an average sized patient, this would equate to 3g of Xepin per application and not more than 12g of Xepin per day. If excessive drowsiness does occur, it may be necessary to reduce the number of applications, the amount of cream applied and/or the percentage of body surface area treated.

Occlusive dressings or clothing may increase the absorption of any topically applied drug, including Xepin; therefore, caution must be exercised when utilising occlusive dressings.

Children under 12 years

There are insufficient data to enable dosage recommendations to be made for children.

Elderly

There are no specific dosage recommendations for elderly patients.

### 4.3 Contraindications

Xepin is contra-indicated in individuals who have shown previous hypersensitivity to any of its components.

## 4.4 Special warnings and precautions for use

Drowsiness may occur with the use of Xepin. Clinical trial data demonstrate that drowsiness is observed principally in patients receiving treatment to greater than 10% of body surface area and that drowsiness is transient, usually remitting after the first few days of treatment. Patients should, therefore be warned of this possibility and cautioned against driving or operating machinery if they become drowsy while being treated with Xepin. Patients should also be warned that the effects of alcohol could be potentiated.

Xepin should be used with caution in patients with glaucoma, a tendency to urinary retention, severe liver disease or mania, in view of the known adverse effects of orally administered doxepin hydrochloride.

## 4.5 Interaction with other medicinal products and other forms of interaction

Alcohol ingestion may exacerbate the potential sedative effects of Xepin particularly in those individuals who use alcohol excessively.

MAO inhibitors should be discontinued at least two weeks prior to the initiation of treatment with Xepin since serious interactions have been reported between orally administered doxepin hydrochloride and MAO inhibitors. As doxepin is metabolised via hepatic microsomal enzymes, care should be taken when co-prescribing any other medicines, which are also metabolised by this route.

Caution should also be exercised in patients being treated with cimetidine since it has been found to affect serum concentrations of orally administered tricyclic antidepressants, such as doxepin hydrochloride.

## 4.6 Pregnancy and lactation

There is inadequate evidence of safety in human pregnancy and lactation. Reproductive studies performed in rats, rabbits, monkeys and dogs with oral doxepin showed no evidence of harm to the animal foetus.

As with all drugs, Xepin should only be used in pregnancy and lactation if, in the clinician's judgement, the benefits outweigh the risks.

## 4.7 Effects on ability to drive and use machines

Patients should be advised not to drive a motor vehicle or operate machinery whilst using Xepin. Particular caution should be exercised during the first few days of treatment.

## 4.8 Undesirable effects

Drowsiness has been reported in clinical trials, with an incidence of 12-19%. However, it is generally of mild to moderate severity and of short duration. Limiting the body surface treated to less than 10% is important in minimising the risk of drowsiness.

Local adverse reactions have been reported with the use of Xepin and may occur more frequently with the use of occlusive dressings. Local reactions, in decreasing order of frequency, include burning, stinging, irritation, and tingling and local rash. Dry mouth has been reported in some patients, but other systemic effects which have been observed with orally administered doxepin such as anticholinergic effects, central nervous effects (other than drowsiness) and gastrointestinal effects are less frequently observed with topical Xepin.

## 4.9 Overdose

Symptoms

Symptoms of overdosage of orally administered doxepin hydrochloride include an increase of any of the reported reactions, primarily excessive sedation and anticholinergic effects such as blurred vision and dry mouth. Other effects

may be pronounced tachycardia, hypotension and extrapyramidal symptoms, but these are unlikely to be seen following topical use.

Treatment

Excess cream should be washed off immediately. Treatment of overdosage is essentially symptomatic. Supportive therapy may be necessary if hypotension and/or excessive sedation occur.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Doxepin hydrochloride is a dibenzoxepin tricyclic compound structurally related to tricyclic antidepressant drugs such as amitriptyline. Doxepin hydrochloride has potent $H_1$ and $H_2$ receptor blocking actions. Histamine is considered to be an important chemical mediator in the pathogenesis of pruritus. Histamine blocking drugs appear to compete at histamine receptor sites and inhibit the biological activation of histamine receptors.

## 5.2 Pharmacokinetic properties

There is a small but noteworthy amount of systemic absorption following topical administration, with wide inter-individual variations in plasma levels and in the handling of doxepin. Orally administered doxepin undergoes extensive first-pass metabolism but topical administration avoids this initial clearance. Plasma doxepin levels following topical administration are generally low, although in a few subjects they may approach the lower limit of the therapeutic range (for depression) of orally administered doxepin.

## 5.3 Preclinical safety data

Doxepin, which is given orally as a tricyclic antidepressant, has been shown to have potent antihistamine activity in animal models. Acute and chronic toxicity of doxepin has been fully evaluated following oral administration to rats and dogs, and these studies revealed the expected effects for this class of drug.

The local toxicity of Xepin has been studied in healthy volunteers. It has been shown to be neither irritant nor allergenic, although it caused local irritation in a small number of cases.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Sorbitol, liquid crystallising
Cetyl alcohol
Isopropyl myristate
Glyceryl stearate
Macrogol stearate
White soft paraffin
Benzyl alcohol
Titanium dioxide
Purified water

## 6.2 Incompatibilities

Not applicable.

## 6.3 Shelf Life

3 years.

## 6.4 Special precautions for storage

Do not store above 25$^{o}$C.

## 6.5 Nature and contents of container

Aluminium tubes with S-22 epoxyphenolic lining and a high density polyethylene spiked screw cap containing 30g, 60g or 120g Xepin. A 6.0g pack is available as a professional sample.

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

No special requirements.

# 7 MARKETING AUTHORISATION HOLDER

Cambridge Healthcare Supplies Limited
14D Wendover Road
Rackheath Industrial Estate
Norwich
Norfolk, NR13 6LH
United Kingdom

# 8 MARKETING AUTHORISATION NUMBER

PA 980/2/1

# 9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1999

Date of last renewal: 01 April 2009

# 10 DATE OF REVISION OF THE TEXT

March 2010