ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

QUITAXON 10 mg, breakable film-coated tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Doxepin hydrochloride ..... 11,31 mg

Equivalent quantity of doxepin ..... 10,00 mg

For one breakable film-coated tablet.

Excipients with known effect: lactose, sunset yellow FCF (E110).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Breakable film-coated tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Major depressive episodes (*i.e.* characterised).

4.2. Posology and method of administration

Use the appropriate dosage of tablet or liquid form depending on the prescribed daily dose.

Posology

The normal dose is very variable depending on the patients (severity of the depressive episode, at-risk patients, etc.). Depending on the circumstances, it is between 10 mg and 300 mg per day, but it can be individually adjusted within the recommended dosing range. This dose may be reassessed after 3 weeks' effective treatment at effective doses.

Antidepressant treatment is symptomatic.

The treatment for an episode is several months (usually about 6 months) to prevent the risks of the depressive episode recurring.

Associated psychotropic treatments

Adding a sedative or tranquillizer treatment can be helpful at the beginning of treatment, to cover the occurrence or worsening of anxiety symptoms. However, tranquillizers do not necessarily protect from inhibition arising.

Paediatric population

No data are available.

Elderly patients

The treatment will be started at low dose, using low dosage forms (see section 5.2). Doses will be increased gradually, if necessary, under clinical monitoring: the side effects of tricyclic antidepressants can have serious consequences in elderly people (falls, confusion).

Hepatic and renal impairment

Dosage reduction may be required (see section 5.2).

Method of administration

The pharmacokinetic properties of this medicine allow it to be taken as a single daily dose, with or without food.

The largest dose can be given in the evening to aid sleep.

4.3. Contraindications

This medicine MUST NEVER BE prescribed in the following cases:

- Hypersensitivity to the active substance or any of the excipients listed in section 6.1.
- Known risk of acute closed-angle glaucoma.
- Risk of urinary retention linked to urethro-prostatic disorders.
- Recent myocardial infarction.
- Combined with sultopride (see section 4.5).

This medicine MUST GENERALLY NOT BE prescribed in the following cases:

- In conjunction with alcohol, clonidine and related medicines, alpha and beta sympathomimetics (adrenaline, noradrenaline, dopamine for systemic action administered by parenteral route) (see section 4.5).

4.4. Special warnings and precautions for use

Warnings and precautions

Suicide/suicidal thoughts or clinical worsening

Depression is associated with an increased risk of suicidal thoughts, self-aggression and suicide (suicidal behaviour). This risk persists until significant remission has been achieved. Since clinical improvement may not occur for several weeks of treatment, patients should be closely monitored until this improvement has been achieved. Clinical experience shows that the risk of suicide may increase at the very beginning of improvement.

Patients with histories of suicidal behaviour or those expressing significant suicidal ideation prior to starting treatment are at a higher risk of experiencing suicidal thoughts or suicidal behaviour and should be closely monitored during treatment. A meta-analysis of placebo-controlled clinical trials of antidepressant drugs in adult patients with psychiatric disorders showed an increased risk of suicidal behaviour with antidepressants compared with placebo in patients less than 25 years old. Close supervision of patients and, in particular, those at high risk should accompany drug therapy especially in early treatment and following dose changes. Patients (and their family members and caregivers) should be alerted to the need to watch for the appearance of a clinical aggravation, suicidal thoughts/behaviours and any abnormal change in behaviour and to seek medical advice if these symptoms occur.

Since rare cases of withdrawal syndrome (headaches, faintness, nausea, anxiety, sleep disorders) have been observed when discontinuing treatment, it is recommended to reduce the doses gradually and monitor the patient particularly carefully during this period.

This medicinal product contains lactose. Patients with galactose intolerance, Lapp lactase deficiency or a glucose-galactose malabsorption syndrome (rare hereditary diseases) should not take it.

This medicine contains an azo colouring agent, sunset yellow FCF (E110), and may cause allergic reactions.

Precautions for use

Insomnia or nervousness at the beginning of treatment may justify reducing the dosage or giving short-term symptomatic treatment.

In the event of a strong manic reaction, doxepin treatment will be discontinued and, in most cases, a sedative neuroleptic will be prescribed.

In epileptic patients or those with a history of epilepsy, it is wise to increase clinical and electrical monitoring, due to the possibility of lowering the seizure threshold. The treatment must be discontinued if seizures occur.

Doxepin should be used with caution:

- In elderly patients presenting:
  - greater sensitivity to postural hypotension and sedation
  - chronic constipation (risk of paralytic ileus);
  - potential prostatic hyperplasia;

- In patients carrying certain cardiovascular disorders, due to quinidine-like, tachycardia-like and hypotensive effects of this product group;

- In cases of hepatic and renal impairment, due to the overdose risk (see section 5.2).

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

Combination with non-selective monoamine oxidase inhibitors is a classic contraindication for all tricyclic antidepressants; the major risk, although poorly documented, is hypo- or hypertensive alterations to blood pressure.

Contraindicated combinations

+ Sultopride

Increased risk of ventricular dysrhythmia, in particular *torsades de pointes*, by addition of electrophysiological effects.

Combinations not recommended

+ Alcohol

Alcohol increases the sedative effect of these substances. Changes in alertness can make driving and operating machines dangerous.

Avoid consuming alcoholic beverages and medicines containing alcohol.

+ Clonidine and related medicines

Described for desipramine and imipramine.

Inhibition and the antihypertensive effect if clonidine (antagonism of adrenergic receptors).

+ Alpha and beta sympathomimetics: adrenaline, noradrenaline, dopamine for systemic action administered by parenteral route

Paroxysmal hypertension with possibility of rhythm disorders (inhibition of adrenaline or noradrenaline entering the sympathetic fibre).

Combinations requiring precautions for use

+ Anticonvulsants

Risk of generalised seizures occurring (seizure threshold lowered by the antidepressant).

Clinical monitoring and potential dose adjustment.

+ Valproic acid, valpromide

Clinical monitoring and potential adjustment of antidepressant dosage.

+ Carbamazepine

Risk of generalised seizures occurring (seizure threshold lowered by the antidepressant, in part), and reduced plasma concentrations of the antidepressant (its hepatic metabolism increased by the anticonvulsant).

Clinical monitoring and potential dose adjustment.

+ Pure serotonergic antidepressants: citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline.

Increase in plasma concentrations of the two antidepressants with risk of convulsions and increased side effects.

Where combined, increased clinical monitoring and, if necessary, dose adjustment (if switching from fluoxetine treatment to a tricyclic antidepressant, the initial dosage will be cautious, increasing it gradually due to the long half-life of fluoxetine and its active metabolite).

+ Alpha and beta sympathomimetics: adrenaline for local haemostatic action by subcutaneous and gingival injection.

Paroxysmal hypertension with possibility of rhythm disorders (inhibition of adrenaline or noradrenaline entering the sympathetic fibre).

Limit the supply, for example, less than 0.1 mg of adrenaline in 10 minutes or 0.3 mg in one hour in adults.

Combinations to be considered

+ Antihypertensives (except clonidine and related medicines)

Antihypertensive effect and increased risk of postural hypotension (additive effects). (Clonidine and related medicines: see combinations not recommended).

+ Atropine and other atropine-like substances: sedative H_1 antihistamines, anticholinergic antiparkinson agents, atropine antispasmodic agents, disopyramide, phenothiazine neuroleptics

Addition of atropine side effects involving urinary retention, constipation, dry mouth, etc.

+ Other central nervous system (CNS) depressants: morphine derivative (analgesics, antitussives and replacement treatments); barbiturates; benzodiazepines; tranquillizers other than benzodiazepines: carbamates, captodiame, etifoxine; hypnotics; neuroleptics; sedative H_1 antihistamines; central antihypertensives; baclofen; thalidomide.

Increased central depression. Changes in alertness can make driving and operating machines dangerous.

+ Baclofen

Risk of increasing muscle hypotonia.

+ Guanethidine (oral route)

Reduction of the antihypertensive effect of guanethidine (inhibition of entry into the sympathetic fibre (site of action).

4.6. Fertility, pregnancy and lactation

Pregnancy

It is desirable to maintain good maternal psychological equilibrium throughout pregnancy. If drug treatment is necessary to provide this equilibrium, it must be started or continued at effective dose throughout the pregnancy, if possible as monotherapy.

To date, while data for doxepin are very limited, they appear to exclude a particular risk of foetal malformation for tricyclic antidepressants. In newborns of mothers treated at the end of pregnancy by a tricyclic antidepressant, signs of absorption (particularly atropinic) and/or withdrawal has sometimes been described:

- neurological disorders in the first week of life (hypotonia, hyperresponsiveness, trembling, exceptionally even convulsions);
- respiratory disorders (polypnoea, onset of cyanosis, exceptionally even respiratory distress);
- digestive disorders (difficulty starting feeding, delayed discharge of meconium and distended abdomen).

All these signs appear in the first days of life and are most frequently mild and short term.

Given these data, it is preferable to avoid using doxepin during pregnancy, irrespective of term. However, treatment must not be stopped abruptly to avoid the risk of severe withdrawal for the mother. If it proves unavoidable to begin or maintain doxepin treatment during pregnancy, consider the effects described above when monitoring the newborn child.

Breast-feeding

Passage into breast milk is poorly understood but probably low; nonetheless, as a precautionary measure, breast-feeding should be avoided throughout the period of treatment.

4.7. Effects on ability to drive and use machines

This medicine may diminish the mental and physical capabilities required for certain hazardous activities, such as operating machinery of driving a car.

4.8. Undesirable effects

Most arise from the pharmacological properties of tricyclic antidepressants.

- **Related to peripheral effects of the molecule:** they are usually mild and generally disappear with continued treatment or a reduction in dose.
  - Anti-cholinergic effects (in decreasing order of frequency): dry mouth, constipation, blurred vision, tachycardia, sweating, urinary problems and possibly urinary retention;
  - Adrenolytic effect: postural hypotension, impotence.
- **Central nervous system effects:**
  - Frequently observed: drowsiness or sedation (antihistamine effect), more marked at the beginning of treatment;
  - Much rarer: trembling, seizures in predisposed patients, transient confused state.
- **Related to the very nature of the depressive illness:**
  - Increase in psychomotor inhibition, with suicide risk;
  - Mood swing with appearance of manic episodes;
  - Reactivation of delirium in psychotic subjects;
    Cases of suicidal ideation and suicidal behaviours have been reported during QUITAXON therapy or early after treatment discontinuation (see section 4.4).
- **Tricyclic antidepressants can also lead to:**
  - Weight gain;
  - Conduction or rhythm problems (with high doses);
  - Endocrine disorders: breast enlargement, galactorrhoea;
  - Hot flushes;
  - Allergic skin reactions;
  - Dysarthria;
  - Exceptional cytolytic or cholestatic hepatitis;
  - Haematological disorders: hypereosinophilia, leukopenia, agranulocytosis, thrombopenia;
  - Syncope.

Some of these undesirable effects can be prevented or combated using adjuvant or corrective therapies, or even by reducing the dose.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the risk/benefit balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system: [French] National agency for safety of medicines and healthcare products (ANSM) and network of Regional Pharmacovigilance Centres - Internet site: www.signalement-sante.gouv.fr.

4.9. Overdose

In cases of deliberate or accidental overdose, severe cardiovascular symptoms are seen (essentially conduction disorders affecting the severity of the poisoning), as well as reinforcement of anticholinergic symptoms, possibly a confused state or coma (sometimes delayed). In this case, the patient should be admitted to hospital immediately in a specialised department for the ingested product to be removed.

Care should include symptomatic treatment and monitoring of vital signs, particularly cardiac and respiratory function for at least five days.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antidepressant / Non-selective monoamine oxidase inhibitor, ATC code: N06AA12.

The biochemical effects, very probably the source of the therapeutic effect, are based on reduced presynaptic uptake of noradrenaline, synaptic transmission of which is facilitated. The sedative affect is related to the histaminergic component of the molecule.

Furthermore, this exerts a central and peripheral anticholinergic effect that causes undesirable effects.

The adrenolytic properties can cause postural hypotension.

The improvement relating specifically to mood is often delayed compared to symptomatic improvements such as ideomotor slowing, insomnia or anxiety. This concept must be considered before interrupting treatment due to inefficacy, as well as adjusting effective doses.

5.2. Pharmacokinetic properties

Metabolism

The liver plays a major role in metabolising tricyclic antidepressants: update (first pass effect) then intense biotransformation, which explains:

- the high plasma clearance value, compared to the hepatic blood flow rate (1.5 L/min);
- the low percentage of active substances found in the urine.

Doxepin is N-demethylated, then after hydroxylation or N-oxidation, the metabolites are glycoconjugated and excreted.

Elimination half-life

The plasma elimination half-life of doxepin is around 10 hours.

Elimination

Excretion is essentially urinary (60%) and faecal.

At-risk populations

- *Elderly patient*: hepatic metabolism decreases and therefore total clearance, increasing steady-state concentration, the free fraction and half-lives. So it is important to reduce doses, at least initially.
- *Hepatic and renal impairment*: it is best to reduce the doxepin dosage.

5.3. Preclinical safety data

Not documented.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Microcrystalline cellulose, lactose (FAST FLO), calcium carboxymethylcellulose, talc, magnesium stearate, anhydrous colloidal silica, sunset yellow FCF (E110) alumina lacquer.

Coating: methylhydroxypropylcellulose with added 10% polyethyleneglycol stearate 300 (SEPPIFILM 3107), yellow iron oxide (E172), titanium dioxide (E171), glycerol, sodium lauryl sulphate.

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

3 years.

6.4. Special precautions for storage

No special precautions for storage.

6.5. Nature and contents of container

40 tablets in blister packs (PVC/Aluminium).

6.6. Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

PROVEPHARM
22 RUE MARC DONADILLE
13013 MARSEILLE, FRANCE

8. MARKETING AUTHORISATION NUMBER(S)

- 34009 333 292 6 6: 40 tablets in blister packs (PVC/aluminium)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 30/04/1990

Date of latest renewal: {DD month YYYY}

10. DATE OF REVISION OF THE TEXT

04/2019

11. DOSIMETRY

Not applicable.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable.

GENERAL CLASSIFICATION FOR SUPPLY

List I