ANNEXES I-II-IIIA-IIIB

ANNEX I

1. NAME OF THE MEDICINAL PRODUCT

VISKEN 5 mg, tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pindolol .....5.0 mg

For 1 tablet

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- High blood pressure.
- Prophylaxis of effort angina attacks.
- Functional signs of obstructive heart disease.
- Treatment of certain arrhythmias: supraventricular (tachycardia, atrial flutters and fibrillations, junctional tachycardia) or ventricular (ventricular extrasystole, ventricular tachycardia).
- Cardiac symptoms of hyperthyroidism

4.2. Dosage and method of administration

Hyperthyroidism, obstructive heart disease: the doses are very variable from one subject to another, most commonly 5–15 mg per day, i.e. 1–3 tablets in 1 or more doses.

High blood pressure: 15 mg per day (3 tablets) on average, which can be administered as a single dose or split doses.

The dose can be increased to 30 mg (2 times 3 tablets).

The maximum dose is 30 mg in one administration and 60 mg per 24 hours.

Arrhythmias: 1–3 tablets per day.

Prophylaxis of effort angina attacks: on average 15 mg per day (3 tablets) in a single dose.

4.3. Contraindications

This medicinal product must never be used in cases of:

- chronic obstructive broncho pneumonia and asthma: non-selective beta-blockers are formally contraindicated in asthmatics (even if the asthma is not currently symptomatic), whatever the dose;
- non-controlled heart failure;
- cardiogenic shock;
- untreated second- and third-degree atrioventricular blocks;
- Prinzmetal angina;
- sinus disease (including atrioventricular block);

- bradycardia (< 45–50 beats per minute),
- Raynaud's phenomenon and peripheral arterial disorders;
- untreated pheochromocytoma;
- hypotension;
- hypersensitivity to pindolol;
- history of anaphylactic reaction;
- combination with floctafenine or with sultopride (see section 4.5).

This medicinal product is generally not recommended during breast-feeding.

4.4. Special warnings and precautions for use

Warnings

Because of the presence of lactose, this medicinal product is contraindicated in cases of congenital galactosaemia, glucose–galactose malabsorption syndrome and lactase deficiency.

The combination of these medicinal products with diltiazem, verapamil or bepridil is not recommended (see section 4.5).

Never stop the treatment suddenly in angina patients: sudden withdrawal can lead to serious arrhythmias, myocardial infarction or sudden death.

Precautions for use

Withdrawal of treatment: the treatment must not be withdrawn suddenly, in particular in patients presenting ischaemic heart disease.
The dose must be progressively reduced, ideally over one or two weeks; the substitution treatment, if necessary, should be started at the same time to avoid an aggravation of the angina.

Heart failure: if necessary, pindolol can be administered to treatment-controlled heart failure patients at very low doses, progressively increasing, under strict medical surveillance.

Bradycardia: if the resting heart rate falls below 50–55 beats per minute and the patient presents symptoms of bradycardia, the dose must be reduced.

First-degree atrioventricular block: given their negative dromotropic effect, beta-blockers must be administered with precaution to patients with a first-degree atrioventricular block.

Pheochromocytoma: the use of beta-blockers in the treatment of high blood pressure due to treated pheochromocytoma requires strict surveillance of arterial pressure.

Elderly subjects: strict respect of the contraindications is imperative in elderly patients. Treatment should be started as low-dose, ensuring close monitoring.

Kidney and liver failure: these can require close monitoring of patients. In practice, the heart rate is monitored; the dose is reduced if excessive bradycardia (<50–55 bpm at rest) appears.

Diabetic subjects: Prevent the disease and reinforce self-monitoring of blood sugar at the start of treatment. The warning signs of hypoglycaemia, in particular tachycardia, palpitations and sweating, can be hidden.

Psoriasis: aggravations of the disease have been reported with beta blockers; the question of utility should be weighed up.

Allergic reactions: In patients susceptible to have a severe anaphylactic reaction, whatever the cause, in particular with iodated contrast agents or floctafenine (see section 4.5) or during desensitising treatments, a beta-blocker treatment can cause an aggravation of the reaction and a resistance to his treatment by adrenaline at normal doses.

General anaesthesia
Beta-blockers will cause an attenuation of the reflex tachycardia and an increase in the risk of hypotension. Continuation of beta-blocker treatment reduces risk of arrhythmia, myocardial ischaemia and hypertensive flushes. The anaesthetist should be warns that the patient is treated with a beta-blocker.

- If it is deemed necessary to stop treatment, a 48-hour suspension could be considered sufficient to allow reappearance of sensitivity to catecholamines.
- In some cases, the beta-blocker treatment cannot be suspended:
  - In patients suffering from coronary artery disease, it is desirable to continue the treatment up until surgery, given the risk linked to sudden withdrawal of beta-blockers.
  - In case of emergency, or the impossibility to withdraw the medication, the patient must be protected from vagal predominance by adequate premedication with atropine repeated according to need. The anaesthesia must use products that are as weakly depressive to the myocardium as possible, and blood losses must be compensated.
- The anaphylactic risk must be taken into account.

Thyrotoxicosis: beta-blockers may hide the cardiovascular signs.

Athletes: athletes' attention is drawn to the fact that this product contains an active substance that could cause a positive reaction to the tests carried out during anti-doping controls..

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

Many medicinal products can cause bradycardia. This is the case for class Ia antiarrhythmics, beta-blockers, some class III antiarrhythmics, some calcium antagonists, digitalis, pilocarpine anticholinesterases, etc.

Contraindicated combinations

+ **Floctafenine**
In case of shock or hypotension due to floctafenine, reduction of cardiovascular compensation reactions by beta-blockers

+ Sultopride
Increased risk of ventricular arrhythmia, notably torsades de pointes.

Combinations that are not recommended

+ Bepridil
Automatism disorders (excessive bradycardia, sinus arrest), sinoatrial and atrioventricular conduction disorders and increased risk of ventricular arrhythmia (torsade de pointes) as well as heart failure.
Such a combination should only be made under strict clinical and ECG supervision, particularly in elderly subjects or at the start of treatment.

+ Diltiazem
Automatism disorders (excessive bradycardia, sinus arrest), sinoatrial and atrioventricular conduction disorders and heart failure.
Such a combination should only be made under strict clinical and ECG supervision, particularly in elderly subjects or at the start of treatment.

+ Verapamil
Automatism disorders (excessive bradycardia, sinus arrest), sinoatrial and atrioventricular conduction disorders and heart failure.
Such a combination should only be made under strict clinical and ECG supervision, particularly in elderly subjects or at the start of treatment.

Combinations subject to precautions for use

+ Amiodarone
Disorders of contractility, automatism and conduction (suppression of sympathetic compensatory mechanisms).
Clinical and ECG surveillance.

+ Baclofen
Increase in the risk of hypotension, especially orthostatic. Monitoring of arterial pressure and dose adaptation of the antihypertensive if necessary.

+ Volatile halogenated anaesthetics
Reduction of cardiovascular compensation reactions by beta-blockers. The beta-adrenergic inhibition can be lifted during the operation by beta-mimetics.
As a general rule, do not stop the beta-blocker treatment and, in all cases, avoid sudden withdrawal. Inform the anaesthetist of this treatment.

+ Clonidine and other central antihypertensives (alpha-methyldopa, guanfacine, moxonidine, rilmenidine)
Serious increase in blood pressure in case of sudden withdrawal of the central antihypertensive treatment.
Avoid sudden withdrawal of the central antihypertensive treatment.
Clinical monitoring.

+ Insulin, hypoglycaemic sulfamides
All beta-blockers can hide certain symptoms of hypoglycaemia: palpitations and tachycardia.
Warned the patients and reinforce self-monitoring of glycaemia, especially at the start of treatment.

+ Lidocaine
With lidocaine used by the intravenous route: increasing plasma concentrations of lidocaine with the possibility of neurological and cardiac undesirable effects (reduction in hepatic clearance of lidocaine).
Clinical surveillance, ECG and, if necessary, monitoring of plasma concentrations of lidocaine during the combination and after the withdrawal of the beta-blocker.
If necessary, adaptation of the dose of lidocaine.

+ Medicinal products causing torsade de pointes (except sultopride: see non-recommended combination): class Ia antiarrhythmics (quinidine, hydroquinidine, disopyramide), class III antiarrhythmics (amiodarone, sotalol, dofetilide, ibutilide), some neuroleptics: (amisulpride, chlorpromazine, cyamemazine, droperidol, fluphenazine, haloperidol, levomepromazine, pimozide, pipamlperone, pipotiazine, sulpiride, tiapride, thioridazine), others: bepridil, cisapride, diphenamil, erythromycin IV, halofantrine, lumefantrine, methadone, moxifloxacin, mizolastine pentamidine, sertindole, spiramycin IV, vincamine IV.
Increased risk of ventricular arrhythmia, notably torsades de pointes.
Clinical and ECG surveillance.

+ Propafenone
Disorders of contractility, automatism and conduction (suppression of sympathetic compensatory mechanisms).
Clinical and ECG surveillance.

Combinations to be taken into account

+ NSAIDs, including selective COX-2 inhibitors
Reduction of the antihypertensive effect (inhibition of vasodilatory prostaglandins by the NSAIDs and retention of water and sodium with pyrazole NSAIDs).

+ Urological alpha-blockers: alfuzosine, doxazosine, prazosine, tamsulosine and terazosine
Increase in the hypotensive effect.
Risk of aggravated orthostatic hypotension.

+ Amifostine
Increase in the risk of hypotension, especially orthostatic.

+ Calcium antagonists: dihydropyridines
Hypotension, heart failure in patients with latent or uncontrolled cardiac insufficiency (addition of negative inotropic effects).
The beta-blocker can also minimise the sympathetic reflex reaction that comes into play in case of excessive haemodynamic repercussions.

+ Imipraminic antidepressants
Increase in the risk of hypotension, especially orthostatic.

+ Alpha blocker antihypertensives (promazine, trimazosine, urapidil)
Increase in the hypotensive effect. Increased risk of orthostatic hypotension.

+ Dipyridamole
With dipyridamole IV: increase in the antihypertensive effect.

+ Glucocorticoids (except hydrocortisone in substitution treatment), Mineralocorticoids, tetracosactide (general route):
Reduction of the antihypertensive effect (retention of water and sodium with corticoids).

+ Neuroleptics
Vasodilator effect and risk of hypertension, especially orthostatic (additive effect).

4.6. Pregnancy and lactation

Pregnancy

Experimental studies in animals have not shown evidence of a teratogenic effect. In the absence of a teratogenic effect in animals, a malformative effect in humans is not expected.

To date, the substances responsible for malformations in humans have proven to be teratogenic in animals during well-conducted studies on two species.

Clinically, no teratogenic effect has been reported to date and the results of controlled prospective studies with some beta-blockers have not shown evidence of birth defects.

In the newborn of a treated mother, the beta-blocker action persists for several days after birth and may result in bradycardia, respiratory distress and/or hypoglycaemia; but most often, this remnant is clinically unimportant.

Nevertheless, heart failure can occur due to production of cardiovascular compensation reactions, requiring hospitalisation in intensive care (see section 4.9), while avoiding solutions to increase blood volume (risk of acute pulmonary oedema).

As a result, this medicinal product, under the normal conditions of use, can be prescribed during pregnancy if necessary. In case of treatment up to childbirth, a close monitoring of the newborn (heart rate and glycaemia during the first 3–5 days of life) is recommended.

Breast-feeding

Beta-blockers are excreted in breast milk (see section 5.2).

The occurrence of hypoglycaemia and bradycardia has been described for certain beta-blockers that are weakly linked to plasma proteins. Because of this, breast-feeding is not recommended if treatment is needed.

4.7. Effects on ability to drive and use machines

Not applicable

4.8. Undesirable effects

Undesirable effects are ranked under headings of frequency, the most frequent first, using the following convention: Very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1000, < 1/100); rare (≥ 1/10,000, < 1/1000); very rare (< 1/10,000), and those whose frequency cannot be determined from the available data.

Cardiac disorders

Indeterminate frequency: Bradycardia, which can be severe; slowing of atrioventricular conduction or intensification of an existing atrioventricular block; heart failure.

Vascular disorders

Indeterminate frequency: Drop in blood pressure; Raynaud's syndrome; cooling of extremities, aggravation of existing intermittent claudication.

Gastrointestinal disorders

Indeterminate frequency: Stomach pain, nausea, vomiting.

Psychiatric disorders

Indeterminate frequency: Insomnia, nightmares.

Respiratory, thoracic and mediastinal disorders

Indeterminate frequency: Bronchospasm.

Metabolism and nutrition disorders

Indeterminate frequency: Hypoglycaemia.

Skin and subcutaneous tissue disorders

Indeterminate frequency: skin rash including psoriasiforme eruption.

Immune system disorders

Indeterminate frequency: Lupic syndrome.

Reproductive system and breast disorders

Indeterminate frequency: Impotence.

General disorders and administration site conditions

Indeterminate frequency: Fatigue.

Investigations

In rare cases, the appearance of antinuclear antibodies has been observed, only exceptionally accompanied by clinical signs such as lupic syndrome and resolving withdrawal of treatment.

4.9. Overdose

In case of bradycardia or excessive low blood pressure, recourse to administration:

- atropine, 1–2 mg IV,
- glucagon 1 mg renewable,
- followed, if necessary, by isoprenaline 25 µg in slow injection or dobutamine 2.5–10 µg/kg/min.

In case of cardiac decompensation in the newborn of a mother treated with beta blockers:

- glucagon on the basis of 0.3 mg/kg,
- admission to intensive care,
- isoprenaline and dobutamine: the dosages (in general high) and the prolonged treatment requires specialist monitoring.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

NON-SELECTIVE BETA BLOCKING AGENT

ATC code: **C07AA03**

Pindolol is characterised by three pharmacological properties:

- the absence of beta-1 cardioselective beta-blocking activity;
- antiarrhythmic activity;
- a strong partial agonist potency (or intrinsic sympathomimetic activity), which allows it to respect the resting heart rate.

5.2. Pharmacokinetic properties

Absorption

Absorption is rapid: the time to reach maximum plasma concentration varies between 1 and 2 hours. Bioavailability is high, 80–95%, practically without hepatic first pass effect, and is not affected by food. The kinetics are linear for doses of 5–15 mg.

Biotransformation

Pindolol is metabolised by the liver (about 50%) and gives rise to inactive conjugated metabolites.

Distribution

The volume of distribution is 2 L/kg.

Pindolol is lipid soluble and crosses the blood-brain barrier.

- *Binding to plasma proteins*: binding to plasma proteins is 50–70%.
- *Elimination half-life*: the plasma elimination half-life of pindolol is 2–4 hours.

Elimination

Pindolol is eliminated by the kidney, and the quantities of unchained products and of metabolites are equivalent (40%). There is a small amount of biliary elimination of metabolites.

Risk situations:

- *Pregnancy*: pindolol crosses the placenta. The ratio between umbilical blood and maternal blood is 0.7;
- *Breast-feeding*: the milk/plasma ratio is 1.6.

5.3. Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose, corn starch, polyvidone excipient, talc, stearic acid, magnesium stearate.

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

50, 90 or 270 tablets in PVC–aluminium blisters

6.6. Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

PHOENIX LABS
SUITE 12
BUNKILLA PLAZA
BRACETOWN BUSINESS PARK
CLONEE
COUNTY MEATH
IRELAND

8. MARKETING AUTHORISATION NUMBER(S)

- 305 426-1: 50 tablets in PVC–aluminium blisters
- 305 426-4: 90 tablets in PVC–aluminium blisters

- 305 426-0: 270 tablets in PVC–aluminium blisters

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[to be completed later by the MA holder]

10. DATE OF REVISION OF THE TEXT

[to be completed later by the MA holder]

11. DOSIMETRY

Not applicable

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Not applicable

PRESCRIPTION AND DISPENSING CONDITIONS

List I (France)