SUMMARY OF THE PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Effortil 5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 tablet contains etilefrine hydrochloride 5 mg.

Excipient: sodium metabisulphite, lactose monohydrate 32 mg per tablet
For complete list of excipients, please see section 6.1.

3 PHARMACEUTICAL FORM

Tablets

Effortil tablets are white and round with bevelled edges. One side is scored and engraved with 05E/05E. The other side is engraved with the company symbol. The diameter of the tablets is 6 mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Symptomatic orthostatic hypotension.

4.2 Posology and method of administration

Adults and children over 7 years: 1-2 tablets 3 times daily.

Children 1-7 years: ½-1 tablet 3 times daily

4.3 Contraindications

Hypersensitivity to the active ingredient or any excipient detailed in section 6.1.

Effortil is contraindicated in patients with hypotensive dysregulation who produce a hypertensive reaction upon standing. In common with other sympathomimetic medical products, Effortil is contraindicated patients with

- hypertension
- thyrotoxicosis
- phaeochromocytoma
- narrow angle glaucoma
- prostate hypertrophy or prostatic adenoma with urinary retention
- coronary disease
- decompensated heart failure
- hypertrophic obstructive cardiomyopathy
- stenosis of the heart valves or central arteries.

Effortil should not be used during the first trimester of the pregnancy (see section 4.6 Pregnancy and lactation).

4.4 Special warnings and special precautions for use

Caution should be exercised when treating patients with tachycardia, cardiac arrhythmias, severe cardiovascular disease, diabetes mellitus or hyperthyroidism.

The tablets contain sodium metabisulphite. Hypersensitivity and bronchospasm may occur.
The tablets also contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

The effects of Effortil may be enhanced by concurrent administration of mineralocorticoids, reserpine, thyroid hormones, other sympathomimetics or any substance with sympathomimetic activity (like tricyclic antidepressants, MAO inhibitors, antihistamins).

Halogenated aliphatic hydrocarbons in inhalational anaesthetics and cardiac glycosides in higher doses may enhance the effects of sympathomimetic agents on the heart and thus lead to the development of cardiac arrhythmias.

Limited data suggest that dihydroergotamine increases the enteral absorption of etilefrine and thereby enhances its action.

Atropine may lead to an enhanced effect of etilefrine and to an increased heart rate.

The blood sugar lowering effect of antidiabetic medication may be decreased.

Alpha- and beta-blocking agents may partially or completely abolish the effects of etilefrine. Treatment with beta-blocking agents can induce reflex bradycardia.

4.6 Fertility, pregnancy and lactation

Pregnancy
Effortil is contraindicated in the first trimester of pregnancy (see section 4.3). Data from a limited number (164) of pregnancies does not indicate an increased frequency of malformations after use of etilefrine during early pregnancy. Preclinical data have demonstrated reproductive toxicity (see section 5.3). Due to its pharmacological effect etilefrine may however impair uteroplacental perfusion and cause uterine relaxation with an increased risk for malformations. During the second and third trimester Effortil should only be used after a careful assessment of risks and benefits with the treatment.

Lactation
There is no information on whether etilefrine passes into breast milk. A risk for an effect on the child cannot be excluded. The mother’s need for treatment with Effortil and the advantages of breast feeding must be weighed against the potential risks for the child.

Fertility
No studies on the effect in human fertility have been conducted. Preclinical studies with etilefrine with respect to fertility have not been conducted.

4.7 Effects on ability to drive and use machines

No studies on the ability to drive and use machines have been performed. As dizziness may occur in certain patients precaution should be taken when driving and using machines.

4.8 Undesirable effects

The adverse effects are presented in falling order of seriousness within each frequency category. The adverse effects frequencies are given according to the following convention: Very common (≥ 1/10), Common (≥1/100, <1/10), Uncommon (≥1/1000, <1/100), Rare (≥1/10 000, <1/1 000), Very rare (< 1/10 000), Not known (cannot be estimated from the available data)

Immune system disorders
Not known: Hypersensitivity reactions

Psychiatric disorders
Uncommon (>1/1000, <1/100): Anxiety, insomnia

Nervous system disorders
Common (≥1/100, <1/10): Headache
Uncommon (≥1/1000, <1/100): Tremor, restlessness

Ear and labyrinth disorders
Uncommon (≥1/1000, <1/100): Dizziness

Cardiac disorder
Uncommon (≥1/1000, <1/100): Palpitations, tachycardia, arrhythmia
Not known: Angina pectoris, blood pressure increased

Gastrointestinal disorders
Uncommon (≥1/1000, <1/100): Nausea

General disorders and administration site conditions:
Not known: Hyperhidrosis

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in

Läkemedelsverket
Box 26
751 03 Uppsala
www.lakemedelsverket.se

4.9 Overdose

Toxicity

100-150 mg to an adult lead to a moderate intoxication. 500-625 mg to both a 4-year-old and an adult gave a severe intoxication.

Symptoms
Anxiety, mydriasis, headache, vomiting (increased intracranial pressure), tremor, possibly cramps. Palpitations, increased blood pressure, possibly reflex bradycardia but tachycardia and possibly arrhythmias at higher doses. Possibly hyperthermia and rhabdomyolysis.

Treatment
Gastric lavage, if justified, coal. In cases of blood pressure increase labetalol is given if need and in addition phentolamin 2.5-5 mg (children 0.05-0.1 mg/kg) i.v. every 5 minutes as needed, thereafter possibly as infusion. In case of pronounced tachycardia metoprolol alternatively atenolol is given. Symptomatic treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: heart stimulating agents, excluding heart glycosides, ATC-code: C01CA01

Etilefrine, the active ingredient of Effortil, is a direct-acting sympathomimetic agent which has a high affinity for alpha1-, and beta1-receptors. Beta2-receptors may also be activated at higher dosages. As a result, it has the ability to enhance cardiac contractility and to raise cardiac output by increasing the stroke volume; in addition, it increases venous tone and central venous pressure and leads to a rise in the circulating blood volume. The positive inotropic effect has been demonstrated in patients with normal or slightly impaired cardiac performance. The drug increases systolic pressure to a greater extent than diastolic pressure, and a slight chronotropic effect was observed. In functional cardiovascular disorders, therefore, the drug can lead to an improvement in subjective symptoms (such as dizziness, tiredness and a tendency to faint) as well as stabilising haemodynamic parameters. Modern clinical effect or safety studies are however not available.

5.2 Pharmacokinetic properties

Absorption
As a result of the first-pass effect, the bioavailability of the tablets is approximately 12%.

Distribution
Approximately 23 % of the drug is bound to plasma proteins. Following a single peroral dose of 10 mg peak plasma concentrations (8 ng/mL) occur after approximately 20 minutes (median) with the tablet, with large intraindividual variability in both C_{max} and t_{max}.

Biotransformation
Etilefrine is primarily eliminated by metabolism. The main metabolite is the sulfuric acid conjugation. There is no evidence to suggest that any of the metabolites are active.

Elimination
The terminal elimination half-life is about 2 hours. Following administration of tritium-labelled etilefrine, 75-80% of the total radioactivity was recovered in the urine. As etilefrine and its conjugates are excreted largely by the renal route, it is possible that the conjugates may accumulate in patients with renal failure.

5.3 Preclinical safety data

In toxicological studies of up to 6 months duration the following effects were seen at oral doses 5-10 times higher than the maximum clinical oral dose:

- decrease in heart rate and blood glucose (rat)
- increased intraocular pressure, mydriasis and increased ALT-levels, fibrotic changes in the myocardium and mitralis valves (rat and dog)
- increased heart weight and hyperplasia of the media in small arteries (dog)

These effects have not been seen in humans, but are judged to be possible in clinical use. Studies regarding carcinogenic potential are lacking.

In mice, rats and rabbits oral doses 25 times higher (15 mg/kg) the clinical maximum dose did not induce foetal death or teratogenic effects. At doses (>30 mg/kg p.o.) toxic to the mother animal, development retardation in rat foetuses was seen, and in mice, a higher incidence of cleft palate and skeletal malformations. These effects are believed to be related to the exaggerated pharmacological effect of etilefrine which causes contraction of vessels in the placenta or of A. uterina media.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Anhydrous colloidal silica
Soluble starch
Sodium metabisulphite (E223)
Glyceryl palmitostearate

6.2 Incompatibilities

Not relevant

6.3 Shelf-life

3 years

6.4 Special precautions for storage

No particular instructions for storage

6.5 Nature and content of container

100 tablets in blister (aluminium/PVC)

6.6 Instructions for use and handling, and disposal (if appropriate)

No particular instructions

7 MARKETING AUTHORISATION HOLDER

Sanofi AB
Box 30052

104 25 Stockholm

8 MARKETING AUTHORISATION NUMBER(S)

5542

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

1958-02-05/2005-07-01

10 DATE OF REVISION OF THE TEX

2017-12-29