Module 1.3.1.1 Summary of Product Characteristics – English version

1. NAME OF THE MEDICINAL PRODUCT

Notaxo 10 mg, orodispergeerbare tabletten
Notaxo 20 mg, orodispergeerbare tabletten

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each orodispersible tablet contains 10 mg ebastine.
Excipient with known effect
Each orodispersible tablet contains 0.21 mg sodium

Each orodispersible tablet contains 20 mg ebastine.
Excipient with known effect
Each orodispersible tablet contains 0.42 mg sodium.

For a full list of excipients, see Section 6.1

3. PHARMACEUTICAL FORM

Orodispersible tablets.

NOTAXO 10 mg are white to off white, round shaped, flat faced bevel edged orodispersible tablets approximately 8.50 mm in diameter and 2.20 mm thickness debossed with ’10’ on one side and plain on the other side.
NOTAXO 20 mg are white to off white, round shaped, flat faced bevel edged orodispersible tablets approximately 11 mm in diameter and 2.70 mm thickness debossed with ’20’ on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

NOTAXO 10 mg
Symptomatic treatment of seasonal and perennial allergic rhinitis, in conjunction with or without allergic conjunctivitis in adults and adolescents aged 12 years and older.
Treatment of urticaria in adults aged 18 years and older.

NOTAXO 20 mg
Symptomatic treatment of seasonal and perennial allergic rhinitis, in conjunction with or without allergic conjunctivitis in adults and adolescents aged 12 years and older.

4.2. Posology and method of administration

For oral use.

Posology

Allergic rhinitis with or without allergic conjunctivitis

For adolescents aged 12 years and older and adults the following dosage recommendations apply:

- 10 mg ebastine (1 NOTAXO 10 mg orodispersible tablet) once daily. In cases of severe symptoms the dose may be increased to 20 mg ebastine (2 NOTAXO 10 mg orodispersible tablets) once daily.
- 10 mg ebastine (1 NOTAXO 10 mg orodispersible tablet) once daily. In cases of severe symptoms the dose may be increased to 20 mg ebastine (1 NOTAXO 20 mg orodispersible tablets) once daily.

[10 mg strength only:]

Urticaria

For adults aged 18 years and older the following dosage recommendations apply:

- 10 mg ebastine (1 orodispersible tablet) once daily.

Special populations

In patients with mild, moderate or severe renal insufficiency or mild to moderate hepatic insufficiency it is not necessary to adjust dose. There is no experience with doses over 10 mg in patients with severe hepatic insufficiency, therefore the dose should not exceed 10 mg in patients with severe hepatic insufficiency.

Treatment may be prolonged until symptoms disappear.

Paediatric population

[10 mg strength only:]

The safety and efficacy of NOTAXO 10 mg in urticaria have not been established in children and adolescents aged 18 years and younger.

The safety and efficacy of NOTAXO 10 mg 20 mg in children aged 12 years and younger have not been established.

Method of administration

The orodispersible tablet should be placed on the tongue where it will disperse. No water or other fluid is required. The orodispersible tablet should be taken out of the blister carefully with dry hands and without crushing it and must be taken straightaway.

Ebastine can be taken with or without food.

Duration of use

The physician decides on the duration of use.

4.3. Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4. Special warnings and special precautions for use

Caution should be exercised when ebastine is administered to patients with known prolongation of the QTc interval on the electrocardiogram, hypokalaemia and in cases of concomitant use of medicinal products known to prolong the QTc interval or inhibit the hepatic CYP450 2J2, 4F12 or 3A4 enzyme system, such as imidazole-type antimycotics and macrolide antibiotics (see section 4.5).

Caution should be exercised in patients with severe hepatic insufficiency (see section 4.2).

Since there is a pharmacokinetic interaction with antimycotics of the imidazole type, like ketoconazole and itraconazole, or macrolide antibiotics, like erythromycin, and antituberculosis agents, like rifampicin (see section 4.5) care should be taken when prescribing ebastine with drugs belonging to such groups.

Excipients
This medicinal product contains less than 1 mmol sodium (23 mg) per orodispersible tablet, that is to say essentially 'sodium-free'.

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

Pharmacokinetic interactions have been observed when ebastine is given with ketoconazole or itraconazole and erythromycin. These interactions resulted in increased plasma concentrations of ebastine and to a lesser extent of carebastine which were, nevertheless, not associated with any clinically significant pharmacodynamic consequences.

Pharmacokinetic interactions have been observed when ebastine is given with rifampin. These interactions could result in lower plasma concentrations and reduced antihistamine effects.

No interactions have been reported between ebastine and theophylline, warfarin, cimetidine, diazepam and alcohol.

The administration of ebastine with food does not cause a modification in its clinical effect.

4.6. Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of ebastine in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development (see section 5.3). As precaution ebastine should not be used during pregnancy unless the indication is compelling.

Breast-feeding
It is not known whether the active substance is excreted in human breast milk. In the rat, excretion of ebastine in milk has been shown. Ebastine should not be used during the lactation period.

Fertility
There are no data on the effects of ebastine on the fertility in humans.

4.7. Effects on ability to drive and use machines

Ebastine has no or negligible influence on the ability to drive and use machines. Most patients treated with ebastine may drive or carry out other activities that require a good reaction capacity. However, in order to identify sensitive subjects who react unusually to ebastine, it is advisable to know the individual reactions before a patient drives or carries out complicated activities: somnolence or dizziness may occur (see section 4.8).

4.8. Undesirable effects

In a pooled analysis of placebo-controlled clinical trials with 5.708 patients on ebastine, the most commonly reported adverse reactions were headache dry mouth and somnolence.
ADRs reported in clinical trials in children (n=460) were similar to those observed in adults.
The table below lists the adverse reactions from clinical trials and post-marketing experience following the convention: very common (≥1/10), common (≥1/100 to < 1/10), uncommon (≥1/1,000 to < 1/100), rare (≥1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

SOCs	Very common	Common	Rare	Not known
Immune system disorders			Hypersensitivity reactions (such as anaphylaxis and angioedema)	
Metabolism and nutrition disorders				Increased appetite
Psychiatric disorders			Nervousness, insomnia	
Nervous system disorders	Headache	Somnolence	Dizziness hypoesthesia, dysgeusia,	
Cardiac disorders			Palpitations, tachycardia	
GI disorders		Dry mouth	Abdominal pain, vomiting, nausea, dyspepsia	
Hepatobiliary disorders			Hepatitis, cholestasis, liver function test abnormal (transaminases, gamma-GT, alkaline phosphatase and bilirubin increased)	
Skin disorders			Urticaria, rash, dermatitis	
Reproductive disorders			Menstrual disorders	
General disorders			Oedema, asthenia	
Investigations				Weight increased

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 Appendix V.

4.9. Overdose

Symptoms
In studies with a high dosage up to 100 mg once daily, no clinically significant symptoms or signs of overdose were seen. Overdose may increase the risk of sedation and antimuscarinic effects.

Treatment
A specific antidote for ebastine is not known.
In the event of overdose, symptomatic treatment as well as monitoring of vital functions, including electrocardiographic monitoring with evaluation of the QT interval for at least 24 hours is indicated. Intensive care may be required in the event of central nervous symptoms developing. Activated charcoal may be given if considered appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Antihistamines for systemic use, other antihistamines for systemic use, ATC code: R06A X22

Mechanism of action
Ebastine is a potent, highly selective antagonist of the histamine H_1 receptor with prolonged effects and no anticholinergic effects.

After oral administration ebastine and the active metabolite pass the blood-brain barrier only to a low extent. This finding is in keeping with the only slight sedating effect found in studies investigating possible effects of ebastine on the central nervous system.

Pharmacodynamic effects
Histamine skin provocation tests revealed a statistically and clinically significant antihistamine effect commencing 1 hour after administration and lasting more than 48 hours.

After ending treatment over a duration of 5 days the anti-histaminergic activity lasted more than 72 hours. This activity is in parallel with the plasma concentration of the most important active metabolite carebastine.

After repeated administration inhibition of the peripheral receptors remained at a constant level without tachyphylaxis. These results suggest that at a dose of at least 10 mg ebastine results in rapid, potent, long-acting inhibition of the peripheral H_1 histamine receptors. This is consistent with a once daily dose.

No significant sedation has been observed at the recommended doses on EEG tests, cognitive performance, sensory-motor coordination and subjective evaluation. At the therapeutically recommended dose there was no significantly intensified sedation. These findings are in keeping with the results of clinical double-blind studies: the frequency of sedative effects of ebastine is comparable with that of placebo.

Following administration at the recommended doses in healthy volunteers, no prolongation of the QT interval or other undesirable cardiac effects were observed in specific studies on the cardiac effects of ebastine.

While no effect of ebastine overdose on the QTc interval was observed with overdoses of up to 60 mg daily, repeated overdoses of up to 100 mg daily or 500 mg as a single dose produced a

statistically significant, but clinically irrelevant increase of 10 ms (2.7 %) and resulted in a slight increase in the heart rate of a few beats per minute. This led to a shortening of the QT interval without a significant effect on the correspondingly corrected QTc interval.

5.2. Pharmacokinetic properties

Ebastine is rapidly absorbed and undergoes extensive first-pass metabolism after oral administration. It is almost totally converted to the active metabolite carebastine. After an oral dose of 10 mg ebastine, maximum plasma levels of 80 to 100 ng/ml carebastine were observed after 2.6 to 4 hours. The half-life of the metabolite is 15-19 hours, 66 % of which is excreted in the urine in the form of conjugated metabolites. After repeated administration of a daily dose of 10 mg, steady-state with plasma levels of 130-160 ng/ml is reached after 3 to 5 days.

After a single dose of 20 mg, the maximum plasma concentration of ebastine is reached after 1 to 3 hours. On average, this concentration is 2.8 ng/ml. The mean maximum plasma concentration of the main metabolite, carebastine, is 157 ng/ml.

The pharmacokinetics of ebastine, as well as that of its active metabolite, carebastine, has been shown to be linear at the recommended therapeutic margin of 10 to 20 mg.
More than 95 % of both ebastine and carebastine is bound to plasma proteins.

In vitro studies on human hepatic microsomes show that ebastine is metabolised to carebastine predominantly via the CYP450 (2J2, 4F12 and 3A4) enzyme systems. After concomitant administration of ketoconazole or erythromycin (both inhibitors of CYP450 3A4) significant increases in plasma ebastine and carebastine concentrations were observed (see section 4.5).

Special patient groups
In elderly patients, no changes in pharmacokinetics were observed compared with young adults.

In patients with mild, moderate or severe renal insufficiency and in patients with mild to moderate hepatic insufficiency treated with daily doses of 20 mg ebastine, the plasma concentrations of ebastine and carebastine on the first and fifth day of treatment were similar to those obtained in healthy volunteers.

In patients with renal insufficiency, the elimination half-life of the metabolite, carebastine is prolonged to 23-26 hours. In patients with hepatic insufficiency, the half-life is 27 hours.

For ebastine film-coated tablets, in cases of concomitant food intake there is a 1.5- to 2.0-fold rise in the plasma level of carebastine, the active principal metabolite of ebastine, and a 50 % increase in the AUC, while T_{max} remains unchanged. However, the clinical efficacy is not affected.

5.3. Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development. Fertility and the duration of gestation were not impaired.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Hypromellose (E464)
Povidone (E1201)
Poloxamer
Gelatin
Carmellose calcium
Crospovidone (E1202)
Mannitol (E421)
Microcrystalline cellulose (E460)
Croscarmellose sodium (E468)
Colloidal hydrated silica (E551)
Trusil peppermint special*
Neotame (E961)
Magnesium stearate (E572)

* Composition: natural flavoring, nature identical flavoring, acacia gum (E414), maltodextrin, sodium benzoate (E211), butylated hydroxyanisole (E320)

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 content of container

OPA/Alu/PVC – Paper/PET/Alu peel-off blisters.

Pack sizes:
20 and 30 orodispersible tablets.
20 and 30 orodispersible tablets.
Not all pack sizes may be marketed.

6.6. Special precautions for disposal <and other handling>

No special requirements.

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

7. MARKETING AUTHORISATION HOLDER

STADA Arzneimittel AG
Stadastrasse 2-18
61118 Bad Vilbel
Duitsland

8. MARKETING AUTHORISATION NUMBER(S)

10 mg: RVG 115463
20 mg: RVG 115466

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Datum van eerste verlening van de vergunning: 9 oktober 2015
Datum van verlenging van de vergunning: 16 juni 2020

10. DATE OF REVISION OF THE TEXT

Laatste gedeeltelijke wijziging betreft de rubrieken 9: 1 april 2020