Annex I

List of the names, pharmaceutical form, strengths of the medicinal products, route of administration, applicant in the Member States

Member State EU/EEA	**Applicant**	**Invented Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Austria	ALFRED E. TIEFENBACHER (GmbH & Co. KG) Van-der-Smissen-Strasse 1 22767 Hamburg Germany	Galantamin STADA 8 mg Retardtabletten	8 mg	Prolonged-release tablet	Oral use
Austria	ALFRED E. TIEFENBACHER (GmbH & Co. KG) Van-der-Smissen-Strasse 1 22767 Hamburg Germany	Galantamin STADA 16 mg Retardtabletten	16 mg	Prolonged-release tablet	Oral use
Austria	ALFRED E. TIEFENBACHER (GmbH & Co. KG) Van-der-Smissen-Strasse 1 22767 Hamburg Germany	Galantamin STADA 24 mg Retardtabletten	24 mg	Prolonged-release tablet	Oral use
Czech Republic	ALFRED E. TIEFENBACHER (GmbH & Co. KG) Van-der-Smissen-Strasse 1 22767 Hamburg Germany	GALASTAD 8 mg	8 mg	Prolonged-release tablet	Oral use
Czech Republic	ALFRED E. TIEFENBACHER (GmbH & Co. KG) Van-der-Smissen-Strasse 1 22767 Hamburg Germany	GALASTAD 16 mg	16 mg	Prolonged-release tablet	Oral use
Czech Republic	ALFRED E. TIEFENBACHER (GmbH & Co. KG) Van-der-Smissen-Strasse 1 22767 Hamburg Germany	GALASTAD 24 mg	24 mg	Prolonged-release tablet	Oral use
Denmark	STADA Arzneimittel GmbH Muthgasse 36 1190 Wien Austria	Galantamin STADA	8 mg	Prolonged-release tablet	Oral use
Denmark	STADA Arzneimittel GmbH Muthgasse 36 1190 Wien Austria	Galantamin STADA	16 mg	Prolonged-release tablet	Oral use

Member State EU/EEA	**Applicant**	**Invented Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Denmark	STADA Arzneimittel GmbH Muthgasse 36 1190 Wien Austria	Galantamin STADA	24 mg	Prolonged-release tablet	Oral use
Finland	STADA Arzneimittel AG Stadastraße 2-18 61118 Bad Vilbel Germany	Galantamine Stada	8 mg	Prolonged-release tablet	Oral use
Finland	STADA Arzneimittel AG Stadastraße 2-18 61118 Bad Vilbel Germany	Galantamine Stada	16 mg	Prolonged-release tablet	Oral use
Finland	STADA Arzneimittel AG Stadastraße 2-18 61118 Bad Vilbel Germany	Galantamine Stada	24 mg	Prolonged-release tablet	Oral use
Ireland	STADA Arzneimittel GmbH Muthgasse 36 1190 Wien Austria	GALANTAX XL 8 mg prolonged-release tablets	8 mg	Prolonged-release tablet	Oral use
Ireland	STADA Arzneimittel GmbH Muthgasse 36 1190 Wien Austria	GALANTAX XL 16 mg prolonged-release tablets	16 mg	Prolonged-release tablet	Oral use
Ireland	STADA Arzneimittel GmbH Muthgasse 36 1190 Wien Austria	GALANTAX XL 24 mg prolonged-release tablets	24 mg	Prolonged-release tablet	Oral use
Portugal	STADA Arzneimittel GmbH Muthgasse 36 1190 Wien Austria	Galantamina Ciclum	8 mg	Prolonged-release tablet	Oral use
Portugal	STADA Arzneimittel GmbH Muthgasse 36 1190 Wien Austria	Galantamina Ciclum	16 mg	Prolonged-release tablet	Oral use

Member State EU/EEA	**Applicant**	**Invented Name**	**Strength**	**Pharmaceutical Form**	**Route of administration**
Portugal	STADA Arzneimittel GmbH Muthgasse 36 1190 Wien Austria	Galantamina Ciclum	24 mg	Prolonged-release tablet	Oral use
Slovak Republic	ALFRED E. TIEFENBACHER (GmbH & Co. KG) Van-der-Smissen-Strasse 1 22767 Hamburg Germany	Galantamine Tiefenbacher 8 mg tablety s predĺženým uvoľňovaním	8 mg	Prolonged-release tablet	Oral use
Slovak Republic	ALFRED E. TIEFENBACHER (GmbH & Co. KG) Van-der-Smissen-Strasse 1 22767 Hamburg Germany	Galantamine Tiefenbacher 16 mg tablety s predĺženým uvoľňovaním	16 mg	Prolonged-release tablet	Oral use
Slovak Republic	ALFRED E. TIEFENBACHER (GmbH & Co. KG) Van-der-Smissen-Strasse 1 22767 Hamburg Germany	Galantamine Tiefenbacher 24 mg tablety s predĺženým uvoľňovaním	24 mg	Prolonged-release tablet	Oral use
Spain	ALFRED E. TIEFENBACHER (GmbH & Co. KG) Van-der-Smissen-Strasse 1 22767 Hamburg Germany	GALANTAMINA Tiefenbacher 8 mg comprimidos de liberación prolongada	8 mg	Prolonged-release tablet	Oral use
Spain	ALFRED E. TIEFENBACHER (GmbH & Co. KG) Van-der-Smissen-Strasse 1 22767 Hamburg Germany	GALANTAMINA Tiefenbacher 16 mg comprimidos de liberación prolongada	16 mg	Prolonged-release tablet	Oral use
Spain	ALFRED E. TIEFENBACHER (GmbH & Co. KG) Van-der-Smissen-Strasse 1 22767 Hamburg Germany	GALANTAMINA Tiefenbacher 24 mg comprimidos de liberación prolongada	24 mg	Prolonged-release tablet	Oral use

Annex II

Scientific conclusions and grounds for refusal

Scientific conclusions

Overall summary of the scientific evaluation of Galantamine STADA and associated names (see Annex I)

- Bioequivalence issues

This procedure concerns a hybrid application (submitted under Art 10(3) of Directive 2001/83/EC as amended) of galantamine containing prolonged release tablets. The reference product is Reminyl 8mg/16mg and 24mg in the form of prolonged release capsules.

The active substance galantamine, a tertiary alkaloid, is a selective, competitive and reversible inhibitor of acetylcholinesterase (AChE). It is indicated for the symptomatic treatment of mild to moderately severe dementia of the Alzheimer type.

Three single dose studies and one steady state study have been conducted to establish bioequivalence of the prolonged release tablets Galantamine STADA in comparison to the reference product Reminyl prolonged release capsules.

The three single dose studies were carried out using the 8 and 16mg strengths:

- A single dose study with the 8 mg dose under fasting conditions
- A single dose study with the 16 mg dose under fasting conditions
- A single dose study with the 16 mg dose after a high fat meal

Single dose studies with the 8 mg and 16 mg formulations demonstrated bioequivalence with the reference product Reminyl (once daily), not only in the conventional bioequivalence range of 80-125%, but in an even tighter range of 90-111% for both AUCt and Cmax. In addition, tmax was in the same range for both products.

A single dose study with galantamine 24 mg was not considered ethically acceptable as such a dose is not given as a first dose to patients. A single dose study with 24 mg was considered to be acceptable due to the poor tolerability of galantamine in patients and in healthy volunteers, provided that the following multiple dose study was performed, which included the 24 mg dose:

- A study at steady state with the highest strength (24 mg) after gradual dose increase (8 mg and 16 mg for 4 days each with dosing after a light meal).

In the study protocol of the multiple dose study, AUC_T and Cmaxss after the 24 mg dose were proposed as primary parameters (for which bioequivalence was shown in the conventional bioequivalence range), while Cminss was not defined as primary pharmacokinetic parameter. Cminss and peak-trough fluctuation (PTF) were considered as secondary parameters as well as all pharmacokinetic parameters for the other two dosage strengths

The multiple dose study was designed to mirror clinical conditions by up-titration of all three doses. All bioequivalence criteria were fulfilled in this study, except for Cmin, which the Applicant originally calculated as the minimum value recorded during 24 hours at steady-state.

Additionally the Applicant also presented as supportive data the peak-trough-fluctuation (%PTF) values for all three strengths and an analysis using repeated measurements of Cmin pd at days 10, 11 and 12 (i.e. at the 24 mg dose) of the multiple dose study.

The intra-subject coefficient of variation (IS-CV) of Cminss was found to be markedly higher in comparison to Cmaxss (37.2 % vs. 11.1% for the 24mg strength). The Applicant explained that the

IS-CV of the single dose studies had been taken into account for the sample size calculation of the multiple dose study and that the study was not powered for the higher IS-CV of Cminss. However the CHMP noted that since the study did not have a replicate design, the IS-CV may in fact also include differences between products and is not true intra-subject CV. The high CV may therefore just reflect a sufficiently large difference between the performance of the compared products. It was also noted that the IS-CV was not as high for the 8mg and 16mg strengths (18% and 25%).

The Applicant was requested by the CHMP to provide justification for the choice of the method for Cmin calculation in the steady state study and also to discuss which definition of Cmin would best reflect the prolonged release characteristics of the product and allow detection of possible differences between test and reference product.

Three definitions of Cmin were discussed:

1) **Cminss** defined as the lowest concentration on a concentration-time curve at steady-state within one dosing interval including the pre-dose concentration value.

2) Cminss defined as the concentration immediately before the 4th dose (**Cpd**)

3) Cminss defined as the concentration 24 h after the 4th dose immediately before the next dose would be administered (**Ctrough**)

Taking into account all the arguments presented, the CHMP agreed that the originally prespecified Cminss values most adequately described the release characteristics of the product in this situation. However none of the 90%CI for this parameter fit into the standard bioequivalence limits.

It was also noted by the CHMP that descriptive Cmin data had already been reported initially. As apparent from the protocol, Cmin (defined as minimum drug concentration in the dosing interval) was pre-specified as secondary parameter (descriptive statistics) and descriptive Cmin data had already been reported in the initial submission. It was clear, that the way for computing Cmin as Cminss was preferred initially, and descriptive statistics for this parameter were submitted in the final study report. The two other ways of calculations (Cpd and Ctrough) were conducted post hoc after it became apparent that prespecified Cminss data did not result in acceptable 90%CI.

The CHMP agreed that although there is no explicit recommendation for computing of Cmin for prolonged release products at the present time, recommendations connected to immediate release products cannot be extrapolated to prolonged release products, which differ from immediate release products with respect to the shape of the pharmacokinetic profile. It was noted that while Cmin and Ctrough should be the same for immediate release products, they usually differ for prolonged release products. In the case of prolonged release formulations, Cmin is usually lower than Ctrough. Furthermore as mentioned previously the Cpd and Ctrough definitions are indeed considered post-hoc, introducing an unacceptable level of bias.

Furthermore the pooling of the pre-dose concentrations (Cmin) in the steady state study at day 10/11/12 as a proof of bioequivalence instead of standard non-pooled data (replicate design), was not considered to be acceptable by the CHMP.

The Applicant also argued that %PTF is in fact a better parameter for the assessment of prolonged release products. However the CHMP highlighted Section 5 of the current CPMP Note for Guidance on Modified Release Oral and Transdermal Dosage Forms (CPMP/EWP/280/96 corr), which states that the following applies for the steady state study:

"Assessment of bioequivalence will be based on AUC_T, Cmax and Cmin applying similar statistical procedures as for the immediate release formulations."

The CHMP were of the view that the requirements of this guideline are clear and they are based on the principle that using a derived parameter (such as %PTF) for the pharmacokinetic evaluation decreases the sensitivity to detect a possible difference between products

The presented results of the single multiple dose steady state study demonstrated that Cmin values after the test product are likely to be substantially lower in comparison to the reference product. This is a product, which is intended to present prolonged release characteristics and therefore the maintenance of sufficient plasma levels is among the main parameters connected to the claimed pharmaceutical form. If the Cmin values of the test product tend to decrease more than in a reference product, one could also expect lower clinical efficacy of the test product.

The CHMP was of the view that Cmin is considered to be an important rate parameter especially in multiple dose bioequivalence studies, and that demonstration of bioequivalence is of paramount importance. In addition the CHMP agreed that the method of analysis should have been clearly indicated in the protocol, and that post-hoc calculations of Cpd and Ctrough were therefore not acceptable.

In addition the CHMP was also of the view that for cholinesterase inhibitors like galantamine, the relationship between administered dose and therapeutic effect is not entirely clear, and for this reason the results from the bioequivalence studies are considered to be of primary importance in this application.

The CHMP concluded that bioequivalence had not been shown and that the pharmacokinetic characteristics suggest inferior performance of Galantamine STADA prolonged release capsules in comparison with the reference product.

The CHMP was therefore of the view that the risk benefit ratio of Galantamine STADA is negative and that a marketing authorization should not be granted.

Grounds for refusal

Whereas

- Bioequivalence in the multiple dose study has not been sufficiently demonstrated.
- The risk-benefit balance is therefore not positive.

the CHMP has recommended the refusal of the granting of the marketing authorisation for Galantamine and associated names (see Annex I).