LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

# Public Assessment Report

# Scientific discussion

**KABERGOLIN IVAX**
**CABERGOLINE RATIOPHARM**
**CABERGOLINE CT**
**CABERGOLINE HEXAL**
**CABERGONICHT**
**KABERGOSTAD**
**KABERGOLIN STADA**
**CABERGOLINE MERCK DURA**
**CABERGODURA**
**CABERGOLINE TEVA**

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**This module reflects the scientific discussion for the approval of Kabergolin IVAX and the duplicates listed above. The procedures for Kabergolin IVAX 1 mg, 2 mg, 4 mg and Cabergonicht 1 mg, 2mg, 4mg were finalised at 21 December 2006. All other procedures were finalised at 17 October 2006. For information on changes after this date please refer to the module 'Update'.**

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.mpa.se E-mail: registrator@mpa.se

# I. INTRODUCTION

IVAX Pharmaceuticals UK Ltd has applied for a marketing authorisation for Kabergolin IVAX tablets 0,5 mg, 1 mg, 2 mg, 4 mg claiming essential similarity to Cabaser and Dostinex marketed in the EU by Pfizer. The product contains cabergoline as active substance. The 0.5 mg tablet strength is indicated for inhibition of lactation for medical reasons, and for treatment of prolactinoma and hyperprolactinaemia. The 1 mg, 2 mg and 4 mg tablet strengths are indicated for treatment of Parkinson's disease, as combination therapy with L-dopa and as monotherapy for newly-diagnosed disease.

The reference product used in the bio-equivalence study is Cabaser tablets 1 mg, manufactured by Pharmacia Laboratories Ltd, UK.

Kabergolin IVAX 0,5 mg, 1 mg, 2mg and 4 mg was first approved in Sweden in May 2004. The duplicates Cabergoline ratiopharm, Cabergoline CT, Cabergoline Hexal, Cabergonicht, Kabergolin Stada, Kabergostad, Cabergoline Merck dura, Kabergodura and Cabergoline Teva were approved for marketing authorisation in Sweden in June 2006. A total of 10 mutual recognition procedures for Kabergolin IVAX and the duplicates were started in July 2006. All procedures for the non-Parkinson's indications (tablet strength 0.5 mg only) were successfully concluded. For two of the procedures involving the indication Parkinson's disease (tablet strengths 1 mg, 2 mg, 4 mg), potential serious risks to public health were raised by two member states at the end of the procedures, and these applications were referred to CMD(h). The potential serious risks to public health concerned that efficacy of cabergoline for the indication Parkinson's disease as monotherapy and as adjunctive therapy to levodopa had not been satisfactorily demonstrated, and a recently identified safety issue for cabergoline, cardiac valvulopathy and subsequent cardiac pathology as a class effect of ergot derived dopamine agonists, and its consequences for the benefit risk of the product.
The objection concerning the efficacy of cabergoline for treatment of Parkinson's disease was resolved during the referral procedure. The issue of cardiac valvulopathy was discussed by the PhVWP at their meeting in December 2006 before the second CMD(h) meeting. In a PhVWP report to the CMD(h), the PhVWP concluded that the increased risk of cardiac valvulopathy associated with cabergoline was at least equivalent to pergolide. The SPC for cabergoline products should therefore be updated in line with the SPC for pergolide products, i.e. restricted second line indication, contraindications and warnings for use and monitoring requirements. The SmPC for Kabergolin IVAX/Cabergonicht was subsequently revised in line with the SmPC for pergolide products and circulated to CMS. The proposal for a revised SmPC was accepted by all CMS. Agreement was therefore reached.

# II. QUALITY ASPECTS

## II.1 Introduction

Karbegolin IVAX is presented in the form of tablets containing 0.5 mg, 1 mg, 2 mg, or 4 mg of cabergoline. The excipients are anhydrous lactose, L-Leucin and magnesium stearate. The tablets are packed in brown glass bottles (type III) that contain a desiccation capsule with silica gel. The brown glass bottle has an induction-sealed childproof aluminium membrane and a childproof HDPE top.

### II.2 Drug Substance

Cabergoline has a monograph in the Ph Eur. Information on carbegoline has been supplied in the form of an ASMF.

Cabergoline is a white or almost white substance, crystalline and exhibits distinct X-ray powder patterns. The structure of cabergoline has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on polymorphism is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

### II.3 Medicinal Product

Karbegolin IVAX tablets are formulated using excipients described in the current Ph Eur. Statements confirming that there is no risk of BSE transmission have been submitted from the suppliers of magnesium stearate and of lactose anhydrous. Magnesium stearate is of vegetable origin. Lactose anhydrous is sourced from healthy animals under the same conditions as milk collected for human consumption. Calf rennet used for production of raw material whey is in accordance with Public Statement EMEA/CPMP/571/02 of February 27 2002.

The product development has taken into consideration the physico-chemical characteristics of the active substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC when stored in the original package in order to protect from moisture.

## III. NON-CLINICAL ASPECTS

### III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

# IV. CLINICAL ASPECTS

## IV.1 Pharmacokinetics

Cabergoline is readily absorbed from the GI-tract and excreted mainly in the faeces as the unchanged compound or metabolites. The $t_{½}$ is approximately 70 h and the kinetics is linear over the therapeutic dose range.

The pharmacokinetic documentation for Kabergolin comprises one bioequivalence study, comparing single doses of Kabergolin 1 mg and the brand leader Cabaser 1 mg after a heavy meal. Single doses of Kabergolin 1 mg tablets and Cabaser 1 mg tablets were found bioequivalent with respect to $C_{max}$, $AUC_{0-t}$, and $AUC_{0-\infty}$.

The applicant was asked to discuss why a 1000 kCal breakfast was given to the subjects and thus justify their study protocol. They responded that the kinetics for cabergoline is known to be linear and is not affected by food. Since cabergoline may cause nausea and vomiting this risk is reduced if the drug is taken with food, it would be unethical to give the drug to the volunteers without food. The response was found acceptable. It is agreed that the heavy meal is not likely to alter the pharmacokinetics in a way that would be clinically relevant. In clinical practice, the drug will be given under steady state conditions where a small difference is absorption rate is not important.

The high extrapolated fraction of AUC (up to 50 % in some individuals) is a weakness in this study. The terminal $t_{½}$ is poorly defined in some cases. There were however no difference between the formulations, and this deficiency is less likely to be of importance for the bioequivalence. The important part of the concentration versus time profile (i.e. the absorption phase) is sufficiently covered.

Table 1. Mean pharmacokinetic parameters per treatment.

| Parameter | Test: Kabergoline IVAX* | Ref: Cabaser* | Point estimate (%) | 90% C.I. (%) |
|---|---|---|---|---|
| $C_{max}$ (ng/ml) | 27.6 (10.3) | 24.1 (8.90) | 115 | 107 - 124 |
| $AUC_{0-t}$ (ng*h/ml) | 1563 (567) | 1517 (510) | 104 | 98.3 - 109 |
| $AUC_{0-\infty}$ (ng*h/ml) | 1972 (739) | 1883 (648) | 105 | 99.2 - 111 |
| $t_{½}$ (h) | 94.0 (31.5) | 90.87 (36.1) | | |
| $t_{max}$ (h) | 1.5 (1) | 2 (2) | | |

*Arithmetic mean (SD) except for $t_{max}$ where median (interquartil range) is given.

## IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

# V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The risk/benefit ratio is considered positive and Kabergolin IVAX tablets 0,5 mg, 1 mg, 2 mg, 4 mg, and the duplicates Cabergoline ratiopharm, Cabergoline CT, Cabergoline Hexal,

Cabergonicht, Kabergostad, Kabergolin Stada, Cabergoline Merck dura, Cabergodura and Cabergoline Teva are recommended for approval.

# Public Assessment Report – Update

| Scope | Procedure number | Product Information affected | Date of start of the procedure | Date of en procedure |
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