PUBLIC ASSESSMENT REPORT
Scientific Discussion

URAPIDIL NORDIC PHARMA 25 mg/5 ml
URAPIDIL NORDIC PHARMA 50 mg/10 ml
Solution for injection

(urapidil)

FR/H/342/01-02/MR

Applicant: Nordic Pharma

Date of the PAR: December 2008
1. INTRODUCTION

Based on review of the quality, safety and efficacy data, the Afssaps has granted a marketing authorisation (MA) for Urapidil Nordic Pharma 25 mg/5 ml and Urapidil Nordic Pharma 50 mg/10 ml, solution for injection from Nordic Pharma on March 1st, 2007.

Urapidil is indicated in the following indication:

Severe hypertension:
- Associated with short term life threatening or internal end organ damage (hypertensive emergency);
- During and/or after surgery

A comprehensive description of the indications and doses is given in the SPC.

This application is a Mutual Recognition Procedure (RMP) with France acting as Reference Member State (RMS), and only involved The Netherlands as Concerned Member State (CMS).

No new preclinical and clinical studies were conducted, which is acceptable as this an abridged application of a generic of Eupressyl, solution for injection initially marketed in France since 1988 by Altana pharma. The clinical data (including pharmacology, pharmacokinetic, clinical and safety) are only based on data from a literature review. According to Note for Guidance CPMP/EWP/QWP/1401/98 from July 2001, the applicant did not submit a bioequivalence study as the product is to be administered as an aqueous intravenous (i.v.) solution containing the same active substance in the same concentration as the currently authorised product.

During this Mutual recognition Procedure (MRP), no potential serious risk to public health concern was raised on the quality, non-clinical, clinical and safety data.

An agreement was found on a common indication (section 4.1) following the review of data from literature. Indeed, indications were initially slightly different between Urapidil Nordic Pharma as proposed by France and another compound only registered in The Netherlands as Concerned Member State (CMS).

The procedure was ended positively and a marketing Authorisation (MA) was granted by The Netherlands (NL) for Urapidil Nordic Pharma 25mg/5 ml and Urapidil Nordic Pharma 50 mg/10 ml, solution for injection.

2. QUALITY ASPECTS

2.1 Introduction

Urapidil Nordic Pharma is a solution for injection containing 25mg/ml and 10mg/ml of drug substance.

The excipients are propylene glycol, sodium dihydrogen phosphate dihydrate, disodium phosphate dihydrate, dilute hydrochloric acid, sodium hydroxide and water for injection.

Urapidil Nordic Pharma is packed in colourless glass ampoules.

2.2 Drug substance
Urapidil is a white crystalline powder soluble in water with no chirality. It is not described in the current Ph.Eur.

The Active Substance Master File (ASMF) procedure is used. Satisfactory scientific data have been provided.

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.

2.3 Medicinal product

Urapidil Nordic Pharma is formulated using excipients described in the current Ph Eur.


The manufacturing process is sufficiently described and critical steps are identified.

Validation of the manufacturing process has been done on industrial batches.

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. The data support the shelf life claimed in the SPC, 3 years with no special storage precautions.

The maximum storage time for Urapidil infusion solutions is 48 hours at 2-8°C and at room temperature, and justified from the chemical and physical in-use stability tests.

3. NON-CLINICAL ASPECTS

Since this product has been shown to be essentially similar to a widely used and well known product based on a full application with regard to preclinical data, no further data have been submitted or are considered necessary, which is adequate.

4. CLINICAL ASPECTS

4.1 Introduction

Urapidil is a well known drug used in France since 1988 to treat severe hypertensive crisis which can occur during or after surgery or in process with short term life threatening.

The pharmacodynamic properties of urapidil on alpha and beta receptors for the peripheral activity and on noradrenergic and dopaminergic receptors for the central activity have been extensively studied and are well known.

In summary, the antihypertensive activity of urapidil is mainly due to the following two mechanisms: i) blockade of vascular postsynaptic alpha-1-adrenoceptors, which leads to a decrease in peripheral resistance; ii) and a central effect clearly different from that of clonidine and related drugs (most likely interaction with 5-HT1A receptors in the brain). In hypertensive patients, these effects are quickly expressed by a reduction in the systolic and diastolic blood pressure, in supine, in upright position, at rest and when in effort with no reflex increase in heart rate. The reduction in blood pressure is secondary to the reduction in the total peripheral resistances (for example at the renal level where the flow-rate increases) with no change in cardiac output. Section 5.1 of the SmPC adequately describes the Pharmacodynamic properties of this antihypertensive agent.

As this is an abridged application, no new clinical trial was performed. Thus, the current clinical dossier (efficacy and safety data) was only based on data from literature.
4.2 Discussion on the clinical aspects

Urapidil efficacy is claimed in two different indications. For each indication, a brief summary of the main efficacy and safety data is summarised thereafter.

Treatment of hypertensive urgencies and emergencies. In hypertensive emergencies, only five studies have been identified between 1993 and 2001. However, in this indication, urapidil is well known in France and has been used by anaesthetists for several years. In the provided trials, urapidil was compared to several reference treatments such as nifedipine sublingual, enalaprilat, sodium nitroprusside, nitroglycerin sublingually in patients with hypertensive urgencies or emergencies (such as encephalopathy, heart failure, angina pectoris, pulmonary oedema, haemorrhagic stroke…). The studies were prospective; mainly with an open label design (only two were randomised). The number of patients included varied from 16 to 168, with a mean age over 60 years. The posology ranged from 12.5 mg to 100 mg, thus including posologies ranging from 25 mg to 50 mg as proposed in the SPC. During these studies, as in clinical practice, when the reduction of blood pressure was not sufficient, the administration of urapidil was repeated. Overall, these data supported the efficacy of urapidil in the indication of hypertensive urgencies and emergencies, with a similar efficacy as standard treatments. Moreover, urapidil significantly reduced systolic and diastolic blood pressures and acted rapidly (the first results were observed in 15 to 45 min).

Treatment of severe hypertension during and/or after surgery. For this indication, urapidil was compared to reference treatments such as clonidine or sodium nitroprussiate in different clinical situations such as cardiac surgery, aortic surgery, neurological surgery or anaesthesia, using different doses of urapidil (from 15 mg to 230 mg, bolus : from 0.4 mg/kg to 2 mg/kg, 100 µg/kg/min). Seven comparative studies were identified; they included from 10 to more than 100 patients. Across all the provided data, the efficacy of urapidil in peri and postoperative hypertensive crisis has been well established. The efficacy of Urapidil in reducing blood pressure in operative situation was demonstrated to be similar to reference products such as clonidine or sodium nitroprussiate, except compared to isosorbide dinitrate. Urapidil acted very quickly, the first results were observed in less than 5 minutes. Reductions in systolic and diastolic blood pressure were maintained after all active treatments for 60 to 720 minutes after the start of infusion.

Specific population: treatment of children and adolescents. Data of the efficacy, safety and the use of urapidil in children are very sparse in literature and limited to one open label study. In this study, the efficacy of urapidil in the treatment of severe postoperative hypertension after cardiovascular surgery was studied in nineteen aged from 12 days to 14 years. Results show that urapidil is effective and safe in the management of hypertension episodes in children during cardiovascular surgery. The posology used in this study is effective and in line with the posology that has been used since numerous years in France. Despite these limited data, urapidil remains to be a useful tool used by pediatricians to treat hypertension urgencies with no major safety concern. Section 4.2 (Posology and method of administration) adequately reflects the posology and use of urapidil in children and adolescents.

The safety profile can be considered as well-established and no product-specific pharmacovigilance issues were identified which are not adequately covered by the current SPC. For the safety concern, the reviewed studies demonstrated the little incidence of side effects; more than 9000 patients have been exposed to urapidil for periods ranging from 4 weeks up to 3 years. Moreover, as it is expected, the adverse reactions are mainly those secondary to blood pressure reduction, i.e. dizziness, headache, nausea and tiredness and, urapidil is globally well tolerated. Specific contraindications for urapidil are unknown. However, as for other vasodilating drugs, intravenous urapidil should not be administered to patients with stenosis of the aortic isthmus or with aortic valve insufficiency. Section 4.8 (Undesirable effects) adequately reflects the safety profile of this product.

4.3 Pharmacokinetics

Despite the fact that the pharmacokinetics data are only based on literature of which articles are rather old, the pharmacokinetic profile of Urapidil is well characterised.
The pharmacokinetic (PK) parameters are well defined after oral or i.v. administration. PK parameters after oral and i.v. administration are similar and are linearly proportional to dose. In summary, after i.v., the plasma concentration decreases for 10 minutes and then remains at that level for about 1 hour. The mean serum half-life of elimination is 2.7 hours. The distribution volume is 0.77 l/kg. The plasma protein binding is 80%. Urapidil is metabolised principally at the hepatic level, into three metabolites, the principal being the inactive parahydroxylated derivative (M1) in humans. 50 - 70 % of the administered dose is eliminated as metabolites in the urine, together with 15 - 20 % of the original product unchanged.

Only two factors modify the pharmacokinetics of urapidil: very old age, severe impairment of liver function. Based on the PK data, no dose adaptation is required in patients with mild to moderate renal or hepatic impairment. In patients with severe renal impairment, a monitoring of hemodynamic changes might be necessary. In patients with severe hepatic impairment, due to the elimination pathway, urapidil is not recommended. A reduction of the dose might only be necessary in elderly, as elderly are more sensitive to this type of treatments, essentially due to the clearance decrease in this population. The corresponding sections of the SPC (4.2, 4.4, and 5.2) adequately reflect the PK parameters of urapidil, including in specific populations.

5. OVERALL DISCUSSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The chemical-pharmaceutical quality of Urapidil Nordic Pharma 25mg/5 ml and 50 mg/10 ml solution for injection from Nordic Pharma is demonstrated, and they are generic forms of Eupressyl IV which is a well-known medicinal product with an established favourable efficacy and safety profile.

No new preclinical or clinical studies were conducted which is acceptable as this is an abridged application. Data from literature adequately demonstrated the efficacy and safety of Urapidil in adults and paediatrics in the two claimed indications.

During the MRP, after review of the overall literature, an agreement was found on the wording of the indication (section 4.1) between the RMS and The Netherlands. Other sections of the SPC, of which 4.2 (Posology and method of administration), 4.6 (Pregnancy and lactation), 4.8 (Adverse effects) and 5.2 (Pharmacokinetic properties) were amended to adequately reflect the efficacy and safety profile of this product. The Package leaflet was adapted accordingly.

The Netherlands as the Concerned Member State mutually recognised the French evaluation of the marketing authorisation. There was no discussion in the CMD(h).

The SPC, Package Leaflet and packaging are in the agreed template and are consistent with the efficacy and safety profile of urapidil.