

Public Assessment Report

Scientific discussion

Metolazon Abcur (Metolazone)

SE/H/890/01/DC

This module reflects the scientific discussion for the approval of Metolazon Abcur. The procedure was finalised at 2010-03-22. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Abcur AB has applied for a marketing authorisation for Metolazon Abcur 5 mg tablets, via an abridged application according to Article 10(3) (Hybrid application), referring to Zaroxolyn 2.5 mg tablets marketed in Sweden by Sanofi-Synthelabo. The product contains metolazone as active substance. For approved indications see the Summary of Product Characteristics. The reference product used in the bio-equivalence study is Metenix 5 mg tablets marketed by (Sanofi-Aventis) in the UK.

II. QUALITY ASPECTS

II.1 Introduction

Metolazon Abcur is presented in the form of tablets containing 5 mg of metolazone. The excipients are microcrystalline cellulose, croscarmellose sodium, lactose monohydrate and sodium stearyl fumarate. The tablets are packed in PVC/Al blister.

II.2 Drug Substance

Metolazone has a monograph in the Ph. Eur.

Metolazone is a white or slightly yellowish, crystalline powder which is poorly soluble in water. The structure of metolazone has been adequately proven and its physico-chemical properties sufficiently described. 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

Metolazon Abcur 5 mg tablets is formulated using excipients described in the current Ph Eur. All raw materials used in the product except lactose monohydrate are of vegetable origin. Lactose monohydrate has demonstrated compliance with Commission Directive 2003/63/EC and the NfG on Minimising the risk of transmitting Animal Spongiform Encephalopathy Agents via human and veterinary medicinal products (EMEA/410/01).

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, with no special storage precautions.

III. NON-CLINICAL ASPECTS

III.1 Discussion on the non-clinical aspects

Metolazone is a well-known substance that has been used clinically for several years. No new non-clinical studies were deemed necessary and the Applicant provided none. Thus, a non-clinical overview of the scientific literature was considered sufficient.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

In a comparative bioavailability study, the Metolazon Abcur 5 mg tablet was compared with Metenix 5 mg tablets from the UK market. Based on composition, Metenix tablets are expected to have a similar bioavailability as the Swedish originator product referred to in the application, Zaroxolyn tablet, which has previously been available as 2.5 mg and 5 tablets but are no longer on the market.

The Metolazon Abcur tablet was shown to be supra-bioavailable compared with Metenix 5 mg tablets. The AUC and C_{max} were 1.8 times and 2.5 times higher after administration of Metolazon Abcur 5 mg than after 5 mg of the reference formulation. The absolute bioavailability of the old Zaroxolyn formulation is in the literature suggested to be around 40-60%. Based on the results from the comparative bioavailability study, the absolute bioavailability of Metolazon Abcur formulation would be expected to be close to 100%.

Breakability of the tablet has been satisfactorily demonstrated. Dose proportionality was shown for AUC between a half and a whole Metolazon Abcur 5 mg tablet, but dose-corrected C_{max} increased somewhat when the tablet was halved. Thus, *half a tablet* of Metolazon Abcur 5 mg would be expected to lead to an AUC that is about 90% and to a C_{max} that is about 140% of the AUC and C_{max} obtained after a dose of 5 mg administered as the reference formulations Metenix/Zaroxolyn tablets.

The effect of concomitant food on the absorption of metolazone from the Abcur formulation is unknown. However, increased bioavailability with food is unlikely, as the absolute bioavailability in the fasted state is expected to be close to 100%. Thereby a potential food effect is no safety issue. As metolazone treatment is started at a low dose, and the dose is individually up-titrated until the desired effect is obtained, a potentially decreased bioavailability with food is also not a problem from an efficacy point of view provided that the concomitant food intake is standardised for the individual patient.

The elimination half-life of metolazone is reported to be 8-10 hours in whole blood and 4-5 hours in plasma. Most of the absorbed drug appears to be excreted in urine, mainly as unchanged substance. Most literature data sources appear to agree that metabolism of metolazone is minimal. Some data indicate that renal excretion of metolazone is directly correlated to creatinine clearance, but there is no study in renal impairment. The lack of such data is, however, acceptable, as metolazone is indicated for patients with renal impairment and

current dosing instructions are based on clinical experience in this group. Moreover, the dose is individually titrated.

The interaction section of the SPC is a combination of the interaction information in the SPCs for the Swedish reference product Zaroxolyn, for the UK product Metenix and for the Swiss metolazone product. As metabolism of metolazone is minimal, the risk for effects of enzyme inhibitors/inducers on metolazone plasma concentrations is expected to be low. The effect of metolazone on drug-metabolising enzymes (inhibition or induction) is unknown. Thus, the SPC includes a warning against concomitant treatment with CYP450 substrates with narrow therapeutic index.

Pharmacodynamics

Metolazone is an organic acid, which is extensively secreted in the kidney by the organic anion secretory pathway and it is active at the luminal surface of both the proximal and distal tubule. The drug causes an inhibition of the re-absorption of sodium in the ascending branch of the loop of Henle and, to a lesser extent, also in the proximal tubules. This leads to a renal excretion of equivalent amounts of sodium and chloride. Metolazone should be titrated and adjusted individually, until the desired therapeutic effect has been reached. The titration is then made according to the effect. In the treatment of renal oedema, 5 mg metolazone of the Metenix product is a common initial dose.

The interactions described in the proposed SPC Section 4.5 are mainly pharmacodynamic interactions.

Clinical efficacy

No new clinical studies were submitted with this application. Four different expert statements on the clinical use of metolazone products have now been submitted in support of the efficacy and safety of the product.

Published study data submitted clearly indicate an effect of metolazone in the treatment of severe oedema in renal disease. Metolazone can potentiate the effect of other diuretics and was in some cases effective also in cases resistant to treatment with other drugs. Most studies referred to do not state what kind of metolazone tablets were used in the study.

Clinical safety

Metolazone has been reported to cause palpitations, chest pain and chills. Severe electrolyte disturbances may occur when metolazone and furosemide are used concurrently. Clinical gout has been reported, occasionally even in patients without previous history of gout attacks. Neutropenia, as well as muscle cramps with impairment of consciousness, have been reported as adverse effects of metolazone. Headache, anorexia, vomiting, abdominal discomfort and dizziness have occasionally been reported as adverse effects. There are also isolated reports of urticaria, leucopenia and tachycardia. Hypotension may occur and may be potentiated by alcohol, barbiturates, narcotics or concurrent therapy with other antihypertensive drugs. Hypercalcaemia may infrequently occur, especially in patients taking high doses of vitamin D or with high bone turnover states. Metolazone should be discontinued before tests for parathyroid function are performed. Thiazide diuretics have exacerbated or activated Systemic Lupus Erythematosus.

Chloride deficit, hyponatraemia and a low salt syndrome may occur during metolazone treatment, particularly when the patient is also on a diet with restricted salt intake. Hypomagnesaemia has been reported as a consequence of prolonged diuretic therapy. Prolonged therapy with metolazone may result in hypokalaemia. The risk of hypokalaemia

increases with higher doses, rapid diuresis, severe liver disease, inadequate oral intake or excess extrarenal losses of potassium (as in vomiting or diarrhea), or with concomitant corticosteroid medication. Hyperuricaemia or azotaemia may occur under metolazone treatment, especially in patients with impaired renal function.

It is recommended that fluid and electrolyte balance should be carefully monitored during therapy, especially if metolazone is used concurrently with other diuretics (especially furosemide), in severe liver disease or co-administration with corticosteroids. The risk of electrolyte disturbances increases at administration of high metolazone doses. Metolazone should be used with caution in elderly patients, patients with impaired renal function plus electrolyte disturbances and in patients on concomitant corticosteroid therapy.

IV.2 Discussion on the clinical aspects

It is a well known fact that different tablet formulations of metolazone have different bioavailability. Since the metolazone dose is individually titrated, it is considered acceptable to refer to efficacy and safety data for the reference product, although absolute bioequivalence has not been demonstrated. Indeed, some of the published data referred to could have been obtained with metolazone formulations with higher bioavailability than Zaroxolyn.

Considering the potency of the drug and the potentially serious adverse effects, the indication has been restricted to patients with oedemas resistant to other therapy, which is adequate.

The minimum recommended dose for the originator Zaroxolyn was 2.5 mg for the indication oedema of heart insufficiency. This would correspond to about a quarter of a Metolazon Abcur tablet, which cannot be administered as the tablet has only one break notch. Thus, the indication oedema of heart insufficiency is not an approved indication for Metolazon Abcur. For the approved indications, the minimum recommended dose is half a Metolazon Abcur tablet.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The user test was assessed in the day 120 AR. In conclusion, the user test was considered acceptable.

The risk/benefit ratio is considered positive and the Metolazon Abcur 5 mg tablets is recommended for approval.

VI. APPROVAL

The decentralised procedure for *Metolazon Abcur 5 mg tablets* was successfully finalised on 2010-03-22.

Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)