

CMDh RECOMMENDATIONS

AZITHROMYCIN CONTAINING MEDICINAL PRODUCTS Severe Hepatic Impairment contraindication

SmPC and PL wording agreed by the CMDh in October 2010

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The CMDh has agreed to request Marketing Authorisation Holders of azithromycin containing medicinal products to amend their SmPC and PIL in accordance with the agreed wording.

SUMMARY OF PRODUCT CHARACTERISTICS

Section 4.4

Since liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with azithromycin (see Section 4.8). Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products.

In case of signs and symptoms of liver dysfunction, such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy, liver function tests/ investigations should be performed immediately. Azithromycin administration should be stopped if liver dysfunction has emerged.

PACKAGE LEAFLET

Section 2: Take special care with Azithromycin

Talk to your doctor before you start to take this medicine if you:

- *have liver problems: your doctor may need to monitor your liver function or stop the treatment*

Section 3: HOW TO TAKE AZITHROMYCIN

Patients with kidney or liver problems:

- *You should tell your doctor if you have kidney or liver problems as your doctor may need to alter the normal dose.*

ANNEX

Introduction

Following a referral discussion for a generic product, at the CMDh, the innovator was requested to discuss whether severe hepatic impairment should be an absolute contraindication or a warning.

Response from the innovator company

To date, there have been no azithromycin studies in patients with severe hepatic impairment. A literature review identified a pharmacokinetic study by Mazzei et al¹ in which the authors concluded no dosage modifications of azithromycin seem to be required for patients with class A or B liver cirrhosis.

The MAH safety database was searched for azithromycin cases, meeting PSUR criteria, received from 04 April 1991 (the International Birth Date) to 31 January 2010 that reported medical history of hepatic impairment, regardless of severity.

Thirty-two cases were identified from the search. The patients in these 32 cases (3 patients with 2 underlying conditions) reported the following medical history PTs (not adverse events): Hepatitis C (10), Hepatitis B (9), Hepatic cirrhosis (7), Hepatic failure (3), Chronic hepatitis (2), Cirrhosis alcoholic (2), Hepatic fibrosis (1), Hepatitis A (1). Of these 32 initial cases, 13 involved patients with potentially severe underlying hepatic impairment (Hepatic cirrhosis, Hepatic failure, Cirrhosis alcoholic, Hepatic fibrosis). Information about the severity of the hepatic impairment in these cases was not available.

Of the 13 cases, 11 were assessed as serious and 2 as non-serious. Five cases were reported from Japan, with the remaining 8 cases from France (4 cases), Korea (2), China (1), and Egypt (1). The demographic information and azithromycin therapy details for this data set are provided below.

Table 1. Azithromycin Cases Reporting Medical History of Hepatic Impairment

		Number of Cases	Percentage
Sex	Female	5	38.5%
	Male	8	61.5%
Age (years) Min = 38, Max = 80 Mean = 56	31-50	5	38.5%
	51-64	4	30.8%
	≥65	4	30.8%
Case Outcome	Recovered/Recovering	7	53.9%
	Recovered with sequelae	1	7.7%
	Not recovered	2	15.4%
	Fatal	2	15.4%
	Unknown	1	7.7%
First Total Daily Dose (mg)	250	1	7.7%
	500	7	53.9%
	600	1	7.7%
First Total Daily Dose (mg)	Intravenous	1	7.7%
	Multiple	3	23.1%
	Oral	8	61.5%
	Unknown	1	7.7%

¹ Mazzei T, Surrenti C, Novelli A, et al. Pharmacokinetics of azithromycin in patients with impaired hepatic function. J Antimicrob Chemother. 1993 Jun;31 Suppl E:57-63.

Most of the adverse events reported by the 13 cases pertain to the General disorders and administration site conditions MedDRA System Organ Class (SOC). Only in 1 case hepatobiliary disorders was reported.

Over half of the patients had recovered or were recovering from the adverse events. Of the 2 fatal cases, the reporting health care professional stated that azithromycin was unrelated to the case outcome in one case (cause of death: ventricular fibrillation). In the second fatal case, the cause of death was reported as respiratory failure and it was the only adverse event reported. This patient had been resuscitated and placed on a respiratory ventilator and renal dialysis before starting treatment with azithromycin and cefoperazone for 2 days.

A review of MAH EU labels includes:

- Text of Section 4.3 and section from 4.4 specific to hepatic impairment from the CSP
- Text from the same sections of the Company Core Datasheet (Company Reference Document)
- A list of the range of azithromycin formulations available
- A summary of SmPC statements, registered products, status of CSP variation, and specific information on severe hepatic impairment in the EU SmPCs

Twenty-seven EU countries have different type of formulations and dosages of azithromycin products approved. Of the 27, only 5 have a contraindication for patients with severe hepatic impairment and these are the only countries that have not yet submitted the variation to update their SmPC in line with the CSP (Greece/Cyprus have submitted, but have not had any feedback as yet). The majority of the azithromycin licenses are longstanding (International Birth Date: 04 April 1991). The recent variations have brought the SmPCs up to date, in line with the guidance and more consistent across the EU.

The MAH is of the opinion that the majority of EU member States agree with the conclusions of the Worksharing PSUR review and the resulting approved CSP and supports the view that advice on the use of azithromycin in patients with severe hepatic impairment should be included in section 4.4 of the SmPC as a warning rather than as a contraindication.

Conclusion:

Based on the review of the safety database and publications from the literature the CMDh concluded that there is no data or safety signal to suggest that use in patients with severe hepatic impairment should never be considered. Therefore, the CMDh considers that inclusion of a special warning in the SmPC and PIL rather than a contraindication, would be more appropriate.