AstraZeneca

3591/IN01

SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Merrem™

ACTIVE INGREDIENT: Meropenem

Trial title (number): Use of meropenem in the treatment of moderate and serious infections (An open, non-comparative, multicentre, post marketing surveillance study)

Developmental phase: IV
First subject recruited: 07 December 2002
Last subject recruited: 13 August 2003
Approval date: 23 February 2004

OBJECTIVES

This study is a Post Marketing Surveillance Study and AstraZeneca, India needs to submit clinical data on 200 patients to the Drugs Controller General of India in order to fulfill Indian regulatory requirements.

Primary Objectives

The primary objective was to assess the clinical efficacy of meropenem in the treatment of moderate to serious hospital infection(s) caused by susceptible pathogens in a large number of Indian patients. Patients with infections at multiple sites were also included and the response of the infection at each site was assessed.

Secondary Objectives

The secondary objectives of the trial were:

(i) to evaluate bacteriological efficacy of meropenem in Indian patients;

(ii) to assess the safety and tolerance of meropenem as measured by:

(a) the incidence of adverse events and

(b) the effect on appropriate haematological and biochemical variables.

Methods:

Study Design: Open, non-comparative, multicentre, post-marketing surveillance (PMS) study

Patient Population: 250 patients from eleven centres enrolled. Patients of either sex, aged 18 years or older, hospitalized and requiring a parenteral antibiotic, with clinical signs and symptoms of a serious infection, caused by pathogens susceptible to meropenem, were included.

Treatment regimen: Meropenem will be given at a dose of 1g 8 hourly, intravenously. Patients suffering from meningitis will be administered a dose of 2g 8 hourly.

Clinical Assessments: The primary endpoint was the clinical response at the end of treatment (including the follow up evaluation for relapse). The secondary endpoints were the clinical response for those patients who were bacteriologically evaluable and the bacteriological response at the end of treatment for evaluable patients. The incidence of adverse events and serious adverse events were recorded.

Results:

Efficacy results

Parameter	Population	N	Yes (%) (Responders)	No (%) (Non responders)	Lower Confidence interval for responders	Upper Confidence interval for responders
Clinical Response	ITT	250	156 (62.4)	96 (37.6)	55.5710	67.6290
Clinical Response	PP	214	156 (72.897)	58 (27.102)	65.9444	77.9809
Bacteriological response	PP	79	51 (64.556	28 (35.443)	50.48	79.71
Clinical response in bacteriological evaluable patients	PP	79	62 (78.48)	17 (21.52)	65.4549	85.2300

EFFICACY

Sixty percent of patients had lower respiratory tract as the main site of infection. Other common main sites of infection included Septicemia (12%), Febrile Neutropenia (11.2%) and Intra-abdominal infections (9.60%). Total 110 patients (43%) had more than one site of infection. Clinical response rate was 62.4 % for Intent to treat (ITT) population [156 of 250 patients, 95% confidence interval 55.57%, 67.62%]. Clinical response rate was 72.9 % patients for per protocol population [156 of 214 patients, 95% confidence interval 65.9%, 77.9%]. Thirty two percent (79 of 250) of total patients were found to be evaluable for bacteriology. For these patients, bacteriological response rate [Success + Presumed Success + Partial success] was 64.56 % [51 of 79 patients]. 49.37% bacteriologically evaluable patients experienced Success, whereas 13.92% patients experienced Presumed Success. 2 patients (2.53%) experienced super infection and 3 patients (3.8%) experienced relapse. 78% of bacteriologically evaluable patients showed clinical response [62 of 79 patients]. 62 patients experienced clinical as well as bacteriological response [78.48%]. Overall response rate observed for meropenem in this study was satisfactory.

SAFETY

A total of 94 adverse events were experienced by 58 (23.2%) patients in this study (From a total of 250 patients). Of these, 83 (88.29%) events were considered as unrelated to study drug, while 11 (11.71%) events were considered to be drug-related. Adverse events due to abnormality in investigations occurred with highest incidence (16.4%) followed by cardiac disorders (4.4%)

and Hepatobiliary disorders (3.6%). Among the actual events reported, Elevated Serum creatinine (4.4%), Abnormal liver function tests (4%), Decreased platelet count (3.2%), Hyperbilirubinemia (2.4%) and Reduced hemoglobin (2%) were more frequently reported adverse events. 46% (43 out of 94) of the total events were mild, 36% (34 out of 94) were moderate and 18% (17 out of 94) were severe. This suggests that nearly 3/4th of the events were mild to moderate. Commonest severe adverse events were Cardiac arrest and Circulatory collapse. All severe adverse events were unrelated to study medication. Among the total events reported, 88.29%(83 out of 94) were considered unrelated to Meropenem.

A total of 54 serious adverse events (SAEs) were recorded during the study. Out of them 52 (i.e. 98%) were not related to the study drug; only 2 (impairment of liver function tests and increased creatinine) were considered to be related to the study drug. As both occurred in the same patient, study drug-related SAEs occurred only in one patient in this study. A total 39 (15.6%) of patients expired during study period. The most common reasons included progressive underlying disease, other co-morbid conditions leading to cardiac arrest of circulatory collapse, or multi-organ failure. None of these were considered to be related to the study drug. An Additional 8 (3.2%) patients died after study and follow up period was over.

In Laboratory analysis, Platelets, WBC, Serum Creatinine showed significant change (improvement) after treatment with antibiotic. This however could indicate a general improvement in patients' condition following recovery from underlying acute sepsis. Increase in Alkaline Phosphatase was statistically significant but not clinically significant. Blood Sugar values at end of treatment were found significantly lower when compared with baseline and appeared to normalize towards end of treatment.

The overall safety data suggests that Meropenem administered at a dose of 0.5 to 1gm 8-hourly was well-tolerated in hospitalized patients with serious infections in this study.

Table S Error! Bookmark not defined. **. Number (%) of subjects who had at least 1 adverse event in any category, and total numbers of adverse events (safety analysis set) .**

Category of adverse event	N (%) of subjects who had an adverse event in each category[a]
Any adverse events	58 (23.2%)
Serious adverse events	29 (11.6%)
Serious adverse events leading to death	2 (0.08%)
Serious adverse events not leading to death	27 (10.8%)
Discontinuations of study treatment due to adverse events	3 (1.2%)
	Total number of adverse events
Adverse events	94
Serious adverse events	54

Table S Error! Bookmark not defined. **. Number (%) of subjects with the most commonly reported[a] adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set).**

Adverse event (preferred term)	Number (%) of subjects who had an adverse event
Serum creatinine increased	11 (4.4%)
Liver function test abnormal	10 (4%)
Platelet count decreased	8 (3.2%)
Hyperbilirubinaemia	6 (2.4%)
Haemoglobin decreased	5 (3%)
Leukopenia NOS	4 (1.6%)
Serum bilirubin increased	4 (1.6%)
Circulatory collapse	4 (1.6%)
Cardiac arrest	4 (1.6%)
Leukocytosis	3 (1.2%)
Atrial fibrillation	3 (1.2%)

a Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

Events with a total frequency of ³1% across all treatment groups are included in this table.

Reference: Listed in Section 10 (Page 75) of CSR

As with any comprehensive clinical trial programme, individual studies may include both approved and non-approved treatment regimens, including doses higher than those approved for clinical use. Before prescribing Merrem™ (Meropenem), Healthcare Professionals should view their specific country information