

Study No: 112281(CM)	
Title: Drug Use Investigation for Clavamox Dry Syrup / Augmentin ES-600(amoxicillin/clavulanate).	
Rationale: This post-marketing surveillance (PMS) collected safety and efficacy data of amoxicillin/clavulanate administered in the Japanese target population per the requirements of the Japanese Pharmaceuticals and Medical Devices Agency (PMDA).	
Phase: Post-Marketing Surveillance (PMS).	
Period: February 2006 ~ May 2006	
Design: Open label, multi-centre, post-marketing surveillance.	
Centres: 127 centres in Japan	
Indication: Otitis media.	
Treatment: All patients received amoxicillin/clavulanate according to the prescribing information in the locally approved label by PMDA.	
Objectives: The study was designed to detect adverse drug reactions (particularly clinically significant adverse drug reactions) occurring in clinical settings, to examine factors likely to affect the safety and efficacy of amoxicillin/clavulanate, and to discuss the need of special investigation and postmarketing clinical study.	
Safety Outcome/Variable(s): Safety outcomes were incidence of adverse events in Japanese pediatric otitis media patients treated with amoxicillin/clavulanate based on prescribing information under the conditions of general clinical practice.	
Efficacy Outcome/Variable(s): Efficacy was assessed on a three-point scale (Improved, Not changed, Worsening) on the basis of the patient's overall condition following the initiation of amoxicillin/clavulanate therapy. Not changed"or W rsening" was judged as not effective..	
Statistical Method: Since this surveillance was not designed to test any statistical hypothesis, basic descriptive statistics were presented.	
Study population: Pediatric subjects who were considered appropriate to prescribe amoxicillin/clavulanate according to the prescribing information were eligible for this surveillance study.	
Number of Subjects:	amoxicillin/clavulanate
Planned, N	400
Entered, N	470
Completed, n (%)	455 (96.8%)
Demographics	
N (ITT safety population)	455
Female (%): Male (%)	53.19:46.81
Age, years, n (%)	
≥5 months - <1	46 (10.11%)
≥1 ~ <7	387 (85.05%)
≥7 ~ ≤11	22 (4.84%)
Japanese, n (%)	455 (100.0%)
Diagnosis, n (%)	
Otitis media	450 (98.90%)
Others	5 (1.10%)
Concomitant disease, n (%)	
Yes	319 (70.11%)
No	135 (29.67%)
Unknown	1 (0.22%)
Concomitant medication, n (%)	
Yes	423 (97.36%)
No	32 (7.03%)
Safety Results: (ITT Safety population)	

Overall incidence of adverse events, n (%)	106 patients, 111 events (23.30%)	
Unexpected adverse events, n (%)	1 (0.22%)	
Serious adverse events, n (%)	2 (0.44%)	
Safety Outcome Variable(s):		
Summary of risk factors by incidence of adverse events	Adverse events, n(%)	
Covariates	Yes (N=106)	No (N=349)
Gender, n (%)		
Male	54 (22.31%)	188 (77.69%)
Female	52 (24.41%)	161 (75.59%)
Diagnosis, n (%)		
Otitis media	106 (23.56%)	344 (76.44%)
Others	0 (0%)	5 (100%)
Most Frequent Adverse Events – On-Therapy, n(%)	Clavamox Dry Syrup (n=455)	
Subjects with any AE(s), n (%)		
Diarrhea	83 (18.24%)	
Abnormal feces	20 (4.40%)	
Vomiting	3 (0.66%)	
Serious Adverse Events -On -Therapy n(%), [n considered by the investigator to be related to study medication]	Clavamox Dry Syrup (n=455)	
	2 (0.44%)	
Subjects with fatal SAE(s)	0 (0.0%)	
<p>Safety: Of the 455 patients included in the Safety Analysis Set, 106 patients had 111 adverse events (AEs) whose causal relationship to Clavamox was not ruled out by the reporting physician (ADRs). The overall incidence of ADRs was 23.30% (106/455 patients). The most frequently reported ADR was diarrhea (83 events), followed by abnormal feces (20 events), vomiting (3 events), cheilitis, nausea, stomatitis, eczema and rash (1 event each). Of the 106 patients with ADRs, only 2 patients reported serious ADRs (2 events of diarrhea). These events were assessed as serious because of disturbed nocturnal sleep associated with frequent diarrhea. Both patients had diarrhea on the treatment start day. In one case, the event improved after discontinuation of Clavamox on the following day; in the other case, the event improved on Day 8 when Clavamox was discontinued. Cheilitis was the only ADR which was unexpected from the prescribing information (precautions for use) for Clavamox. Patients with cheilitis concurrently had stomatitis and eczema. All these events were not serious and resolved at the completion of 11-day continuous treatment.</p>		

Efficacy Results:		
	Effective	Not Effective
Overall Efficacy Results, n (%)	412 (95.15%)	21 (4.85%)
Otitis media, n (%)	412 (95.15%)	21 (4.85%)
Efficacy Outcome Variable (s)		
Gender, n (%)		
Male	216 (92.70%)	17 (7.30%)
Female	196 (98.00%)	4 (2.00%)
Hospitalisation status, n (%)		
In-patients	1(100.00%)	0 (0%)
Out-patients	411 (95.14%)	21 (4.86%)
Concomitant medications, n (%)		
Yes	382 (95.26%)	19 (4.74%)
No	30 (93.75%)	2 (6.25%)

Efficacy: The overall efficacy rate in the 433 patients of the Efficacy Analysis Set was 95.15% (412/433 patients). A subgroup analysis by type of otitis media showed an efficacy rate of 95.47% (400/419 patients) for "acute and purulent", 100.00% (2/2 patients) for "chronic and purulent" and 88.89% (16/18 patients) for "exudative".

Conclusion: The overall incidence of ADRs in the 455 patients of the Safety Analysis Set was 23.30% (106/455 patients). There were two serious adverse events (2 events of diarrhea), and one unexpected adverse event was reported. The overall efficacy rate in the 433 patients of the Efficacy Analysis Set was 95.15% (412/433 patients).

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