

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: No product related

ACTIVE INGREDIENT: Not applicable

Study No: NIS-GES-DUM-2008/3 (NCT00717118)

Evaluation of the Effect of the Association of Proton Pump Inhibitor (PPIs) With Non-Steroidal Anti-Inflammatories (NSAIDs) in Work Leave Time.

Developmental phase: Phase IV

Study Completion Date: 01/03/2009 (DBL)

Date of Report: 01/04/2009

OBJECTIVES:

Main objective:

To describe the impact on work leave, measured by the reduction in **work leave time**, of Proton Pump inhibitor (PPI), Omeprazole, when is associated with a Non-Steroidal Anti-Inflammatory Drug (NSAID).

Secondary Objectives:

1. To describe the rate of **gastrointestinal complications** in patients with or without PPI's treatment (Omeprazole) associated with NSAID.
2. To estimate the difference in **medical consultations** in patients with or without PPI's treatment (Omeprazole) associated with NSAID.

METHODS:

Study design:

Descriptive, retrospective, cohorts' study. Source of information: Ibermutuamur's (Mutual Work Insurance Company) medical records database. Two different cohorts (treatment groups) have been defined according to the following criteria:

- Patients with associated PPI treatment (Omeprazole)
- Patients without associated PPI treatment (Omeprazole)

The follow-up period were from the date of the occupational accident to the date of final discharge related to the diagnosis that implies the prescription of NSAIDs.

Study population:

- Patients who have suffered a sprain of ankle (ICD-9, 845.0), and
- Patients with date of discharge from January 1, 2007 to December 31, 2007, and
- Patients with a prescription of a NSAID with or without an associated PPI (Omeprazole), as result of the occupational accident.

If the occupational accident did not cause in a work leave in the first visit, then it must result in a work leave in sometime during the follow-up period.

Statistical methods:

Due to the study design, variables were presented by descriptive statistics. Categorical data were reported as frequencies and proportions. Continuous data were reported as means and standard deviations. Where appropriate, alternative descriptive statistics such as quartile ranges, and medians with ranges for categorical and continuous data respectively were reported.

A single-factor fixed-effect analysis of covariance (ANCOVA) model, including history of peptic ulcer or other GI complications as confounding factors, was created to compare days of work leave between treatment groups. In the same way, another similar model was created to compare the number of medical consultations during the study follow-up.

An adjusted logistic regression model, adjusting for history of peptic ulcer or other GI complications, was created to estimate the risk of GI complications during the study follow-up between exposed (NSAID+Omeprazole) versus unexposed (NSAID).

RESULTS:

Descriptives and crude differences between treatment groups:

	N	(%)
NSAID + Omeprazole	2128	41.00%
NSAID	3062	59.00%
TOTAL	5190	100.0%

The study sample included 5,190 evaluable patients. 59% of the patients not treated with an associated PPI (Omeprazole).

Table 2 Sex			
	N	(%)	95CI%
Man	3982	76.7%	(75.6%,77.9%)
Woman	1208	23.3%	(22.1%,24.4%)
TOTAL	5190	100%	(100%, 100%)

Sex vs. Treatment group			
	NSAID + Omeprazole	NSAID	Total
Man	1610 (75.66%)	2372 (77.47%)	3982 (76.72%)
Woman	518 (24.34%)	690 (22.53%)	1208 (23.28%)
TOTAL	2128 (100%)	3062 (100%)	5190 (100%)

p-value (Chi-square)=0.1296

The majority of patients were male, 77%, with no statistical differences observed between treatment groups.

Table 3 Age (years)		
N	Mean ± SD*, 95CI%	Median (IQR**), [Min,Max]
5190	35.11±10.53, (34.82,35.39)	33.00 (15.00), [18.00,67.00]

Age (years) vs. Treatment group				
Group	N	Mean ± SD*	95CI%	P-value (Student's-t)
(1) NSAID + Omeprazole	2128	36.85±10.77	(36.41,37.29)	
(2) NSAID	3062	33.90±10.20	(33.53,34.27)	
Difference (1 - 2)		2.95	(2.37,3.53)	P=<.0001

**SD=Standard Deviation*
***IQR=InterQuartile Range*

The overall mean age was 35 years, ranging from 18 years to 67 years. Statistically significant differences between treatment groups have been observed, with the older patients, a mean age of 37, in the NSAID+Omeprazole group, versus a mean age of 34 in the NSAID group.

Table 4 Previous history of peptic ulcer

	N	(%)	95CI%
Yes	70	1.35%	(1.06%,1.70%)
No	5120	98.65%	(98.30%,98.94%)
TOTAL	5190	100%	

Previous history of peptic ulcer vs. Treatment group

	NSAID + Omeprazole	NSAID	Total
Yes	34 (1.60%)	36 (1.18%)	70 (1.35%)
No	2094 (98.40%)	3026 (98.82%)	5120 (98.65%)
TOTAL	2128 (100%)	3062 (100%)	5190 (100%)

p-value (Chi-square)=0.1948

Previous history of peptic ulcer was present in only 1% of the patients, with no significant differences between treatment groups.

Table 5 Previous history of other GI complications

	N	(%)	95CI%
Yes	228	4.39%	(3.86%,4.98%)
No	4962	95.61%	(95.02%,96.14%)
TOTAL	5190	100%	

Previous history of other GI complications vs. Treatment group

	NSAID + Omeprazole	NSAID	Total
Yes	133 (6.25%)	95 (3.10%)	228 (4.39%)
No	1995 (93.75%)	2967 (96.90%)	4962 (95.61%)
TOTAL	2128 (100%)	3062 (100%)	5190 (100%)

p-value (Chi-square)<0.0001

The proportion of patients with previous history of other Gastrointestinal (GI) complications was 4.4%. There were statistically significant differences between treatment groups, with a proportion of patients reporting previous history of other GI complications of 6.3% in the NSAID+Omeprazole group, versus 3.1% in the NSAID group.

Table 6 Work leave (days)

N	Mean ± SD*, 95CI%	Median (IQR**), [Min,Max]
4480	16.99±25.89, (16.23,17.75)	11.00(14.00), [0.00,722.00]

Work leave (days) vs. Treatment group

Group	N	Mean ± SD*	95CI%	P-value (Student's-t)
(1) NSAID + Omeprazole	1815	18.94±28.04	(17.75,20.13)	
(2) NSAID	2665	15.66±24.24	(14.68,16.64)	
Difference (1 - 2)		3.28	(1.74,4.83)	P=<.0001

*SD=Standard Deviation

**IQR=InterQuartile Range

Overall mean days of working leave were 17 days. Statistically significant differences between treatment groups have been observed, with a mean of 19 days, in the NSAID+Omeprazole group, versus a mean of 16 years in the NSAID group.

Table 7 GI complications

	N	(%)	95CI%
Yes	23	0.44%	(0.29%,0.66%)
No	5167	99.56%	(99.34%,99.71%)
TOTAL	5190	100%	

GI complications vs. Treatment group

	NSAID + Omeprazole	NSAID	Total
Yes	18 (0.85%)	5 (0.16%)	23 (0.44%)
No	2110 (99.15%)	3057 (99.84%)	5167 (99.56%)
TOTAL	2128 (100%)	3062 (100%)	5190 (100%)

p-value (Chi-square)=0.0003

The percentage of appearance of GI complications during the study follow-up was 0.4%. There were statistically significant differences between treatment groups, with a proportion of patients reporting appearance of GI complications of 0.9% in the NSAID+Omeprazole group, versus 0.2% in the NSAID group.

Table 8 Medical consultations				
N	Mean ± SD*, 95CI%		Median (IQR**), [Min,Max]	
5184	4.14±3.28, (4.05,4.23)		3.00(3.00), [1.00,80.00]	
Medical consultations vs. Treatment group				
Group	N	Mean ± SD*	95CI%	P-value (Student's-t)
(1) NSAID + Omeprazole	2125	4.56±3.90	(4.42,4.70)	
(2) NSAID	3059	3.85±2.72	(3.73,3.96)	
Difference (1 - 2)		0.71	(0.53,0.89)	P=<.0001
*SD=Standard Deviation				
**IQR=InterQuartile Range				

The overall mean of medical consultations during the study follow-up was 4.1 consultations, with a median of 3 consultations. Statistically significant differences between treatment groups have been observed, with a mean of 4.6 consultations, in the NSAID+Omeprazole group, versus a mean of 3.9 consultations in the NSAID group.

Multivariate analyses:

All models creation and selection was based on *a priori* clinical considerations.

Primary endpoint:

Table 9 Work leave (days) – ANCOVA Model				
Treatment group	Adjusted Means*	Means Difference		p-value
		Difference	95CI%	
NSAID + Omeprazole	19.27	3.16	(1.62; 4.70)	<0.0001
NSAID	16.11			
* Least Squares Means. LS-Means				

There has been observed a statistically significant difference of more than 3 days between treatment groups.

First secondary endpoint:

Table 10 GI complications – Adjusted Logistic Regression			
Treatment group	Adjusted OR	95CI%	p-value
NSAID + Omeprazole (exposed)	5.135	(1.899,13.884)	0.0013
NSAID (unexposed)			

The risk of GI complications during the study follow-up was significantly higher (OR: 5.1) in the NSAID+Omeprazole group versus the NSAID group.

Second secondary endpoint:

Table 11 Medical consultations – ANCOVA Model				
Treatment group	Adjusted Means*	Means Difference		p-value
		Difference	95CI%	
NSAID + Omeprazole	4.61	0.71	(0.53,0.89)	<0.0001
NSAID	3.90			

* *Least Squares Means. LS-Means*

There has been observed a statistically significant difference of 0.7 medical consultations between treatment groups.