Clinical Study Report Synopsis	
Drug Substance	NA
Study Code	NIS-GGR-DUM-2008/1
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TITLE:
UPPER GI SYMPTOMS IN PATIENTS RECEIVING ACETYLSALICYLIC ACID/NSAIDs – NSAIDs WAVE 2 (NSAIDs II)

Study dates: First patient enrolled: 21 March, 2008
Last patient completed: 20 June, 2008

Phase of development: NA (Observational NIS study)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study protocol.

Abbreviation or special term	Explanation
BMI	Body Mass Index
GERD	Gastroesophageal Reflux Disease
GI	Gastrointestinal
H_2RA	H_2 receptor-antagonist
NA	Not Available
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PPI	Proton Pump Inhibitor
SD	Standard Deviation

Study centre(s)

85 primary care office-based physicians (internists, orthopaedics, cardiologists and rheumatologists).

Publications

Not applicable

Objectives

- To assess the nature and frequency of upper GI symptoms (Dyspepsia and GERD) experienced by patients receiving acetylsalicylic acid (aspirin) and/or NSAIDs.
- To record the main indications for aspirin and/or NSAIDs prescription among office based primary care physicians in Greece.
- To record the current clinical practice in terms of gastroprotection in patients receiving acetylsalicylic acid and/or NSAIDs.

Study design

Observational, cross-sectional, single visit, non-interventional study.

Target patient population and sample size

The study sample consisted of the first 10 consecutive patients visiting one of the participating office based primary care physicians, being at least 18 years of age and receiving NSAIDs and/or acetylsalicylic acid over at least 5 days of one week during the last month before the study's single visit.

The study enrolled 850 patients. Out of the 850 patients, 48 were not included in the analysis due to either violation of the inclusion/exclusion criteria or due to incomplete data.

Duration of treatment

Not applicable. All data for the study population were collected in a single visit.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Not applicable

Criteria for evaluation - Main variables

Primary variable

- Frequency (%) of patients in the primary care setting, presenting upper GI symptoms while receiving NSAIDs/Acetylsalicylic acid treatment with/without gastroprotective measures.

Secondary variables

- The nature of upper GI symptoms (Dyspepsia and GERD) experienced by patients receiving acetylsalicylic acid and/or NSAIDs treatment.
- Main indications for acetylsalicylic acid and or NSAIDs prescription among private practice office based physicians in Greece.

Other variables

- Chronic diseases in the study population
- Concomitant treatments
- Percentage of patients receiving antacids, H_2RAs and PPIs as gastroprotective treatment.
- Percentage of patients experiencing GERD symptoms due to acetylsalicylic acid and/or NSAIDs administration.
- Percentage of patients experiencing dyspepsia symptoms due to acetylsalicylic acid and/or NSAIDs administration.
- Days of upper GI symptoms in patients:
    - Receiving no gastroprotection
    - Receiving H_2RA/antacids
    - Receiving PPIs
- Helicobacter Pylori infection information.

Patient-reported outcomes (PROs)

A structured questionnaire assessing the frequency of upper GI symptoms during the last week prior to the study visit was completed by the study subjects.

Criteria for evaluation - safety

Not applicable.

Statistical methods

Descriptive statistical methodology was applied for all study variables.

Summary of results

Baseline Characteristics

Eight hundred and two (802) evaluable patients were enrolled and analyzed in the current study. Baseline patient characteristics are presented in Table 1.

Table 1. *Patients' demographics*

Sex		
Male (n, %)	342, 43.1	(n=792)
Female (n, %)	452, 56.9	
Age (mean ± sd) [years]	57.7 ± 14.1	(n=797)
BMI (mean ± sd) [krg/m^2]	26.9 ± 3.7	(n=798)

GI medical history and other medical history

The most prevalent chronic disease of the study population was arterial hypertension (48.6%) followed by cardiovascular diseases (21.6%) and diabetes mellitus (16.4%), whereas 31.4% of the patients presented with no chronic disease (Table 2).

Table 2. *Patients' medical history*

	N	%
No history	251	31.4
Arterial hypertension	389	48.6
Cardiovascular diseases	173	21.6
Diabetes mellitus	112	16.4
Respiratory diseases	94	11.8
Other diseases	157	19.6
NA	*3*	

Prior to administration of NSAIDs/Acetylsalicylic acid, 51.5% of patients did not have any GI medical history, while 20.5% had a prior diagnosis of GERD (Table 3).

Table 3. *GI history prior to administration of NSAIDs/Acetylsalicylic acid*

	N	%
No history	412	51.5
GERD	164	20.5
Ulcer	107	13.4
Esophagitis	100	12.5
Hiatus hernia	66	8.3
Other	34	4.3
Complications of ulcer	9	1.1
NA	*2*	

Concomitant medications

At the time of the study, 23.9% of patients were not receiving other medications in combination with NSAIDs and/or acetylsalicylic acid (Table 4); medications to treat hypertension and dyslipidemia were those with the highest frequencies (48.7% and 26.1%, respectively).

Table 4. *Concomitant medications*

	N	%
None	189	23.9
Antihypertensives	386	48.7
Antilipidemics	207	26.1
Antibiabetics	124	15.7
Muscle relaxants	96	12.1
Antithrombotic agents	92	11.6
Antiosteopenic agents	84	10.6
Corticosteroids	65	8.2
Antibiotics	53	6.7
Anticoagulants	46	5.8
Immunosupressants	17	2.1
Monoclonal antibodies	7	0.9
Cytostatics	7	0.9
Other	78	9.8

Helicobacter Pylori Information

Almost 28% of patients had been tested for *Helicobacter pylori,* whereas 19.5% were found positive and had received eradication treatment (Table 5).

Table 5. *Helicobacter pylori test & treatment*

	N	%
Patients Tested for Helicobacter pylori		
No	562	72.2
Yes	216	27.8
positive received treatment	152	19.5
positive not received treatment	33	4.2
positive, treatment status: unknown	31	4.0
NA	*24*	

Main indications for NSAIDs/Acetylsalicylic acid use

The main indications for NSAIDs/Acetylsalicylic acid use in the study population were musculoskeletal diseases (39.8%), low back pain (18.4%), osteoarthritis (15.9%) and cardiovascular diseases (12.5%) (Table 6).

Table 6. *Main Indications for NSAIDs/Acetylsalicylic acid*

	N	%
Musculoskeletal Diseases	301	39.8
Low Back Pain	139	18.4
Osteoarthritis	120	15.9
Cardiovascular Diseases	95	12.5
Coronary Heart Disease	65	8.6
Rheumatoid Arthritis	25	3.3
Pain	15	2.0
Headache	14	1.8
Rheumatic Diseases	8	1.1
Neoplastic Diseases	3	0.4
GI Tract Diseases	1	0.1
Psychiatric Diseases	1	0.1

Duration of NSAIDs/Acetylsalicylic acid use is tabulated in the following table, with most patients receiving NSAIDs for 5 days in 1 week during the last month prior to the study visit (Table 7).

Table 7. *NSAIDs/Acetylsalicylic acid use prior to the study*

	N	%
Acetylsalicylic acid 5 days in one week during last month	198	26.5
Acetylsalicylic acid 5 days/week for at least 3 months	212	27.5
NSAIDs 5 days in one week during last month	579	75.5
NSAIDs 5 days/week for at least 3 months	186	26.0

Frequency of upper GI symptoms

The most frequently reported upper GI symptoms in the study population were heartburn, epigastric pain and regurgitation (Table 8).

Table 8: *Frequency of reported upper GI symptoms in the study population*

	No Symptoms*		2 days/w		3-5 days/w		6-7 days/w		*NA*
	N	%	N	%	N	%	N	%	
Heartburn	372	50.6	106	14.4	221	30.1	36	4.9	*67*
Regurgitation	418	57.3	103	14.1	188	25.8	21	2.9	*72*
Epigastric pain	405	55.6	88	12.1	214	29.4	22	3.0	*73*
Early satiety	503	72.3	67	9.6	117	16.8	9	1.3	*106*
Postprandial fullness	473	67.6	78	11.1	136	19.4	13	1.9	*102*
Nausea	587	84.3	48	6.9	59	8.5	2	0.3	*106*
Vomiting	632	89.4	30	4.2	42	5.9	3	0.4	*95*
Bloating	522	74.6	67	9.6	103	14.7	8	1.1	*102*
Belching	425	59.4	88	12.3	181	25.3	21	2.9	*87*

* No symptoms or symptoms for 1 day in the last week prior to the study visit

GERD-symptoms were reported by 59.4% of patients, while 70.8% of them reported dyspepsia symptoms. Overall, upper GI symptoms (GERD and/or dyspepsia) for 2 or more days per week were reported by 80.6% of the participants (Table 9).

Table 9. *Proportion of patients with GERD, dyspepsia and upper GI symptoms*

	N	%
GERD symptoms[1]	450	59.4
Dyspepsia symptoms[2]	536	70.8
Upper GI symptoms[3]	626	80.6

1. *GERD symptoms: heartburn and/or regurgitation.*
2. *Dyspepsia symptoms (at least one of): epigastric pain, early satiety, postprandial fullness, nausea, vomiting, bloating, belching.*
3. *Upper GI symptoms (at least one of): heartburn, regurgitation, epigastric pain, early satiety, postprandial fullness, nausea, vomiting, bloating or belching.*

The frequency of GERD, dyspepsia and upper GI symptoms is shown in table 10.

Table 10. *Frequency of GERD, dyspepsia and upper GI symptoms*

	No Symptoms*		**2 days/w**		**3-5 days/w**		**6-7 days/w**		*NA*
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
GERD symptoms	307	40.6	124	16.4	278	36.7	48	6.3	*45*
Dyspepsia symptoms	221	29.2	117	15.5	366	48.3	53	7.0	*45*
Upper GI symptoms	151	19.4	126	16.2	419	53.9	81	10.4	*25*

* No symptoms or symptoms for 1 day in the last week prior to the study visit

Study subjects were requested to report their dominant upper GI symptom. Heartburn was reported as the dominant upper GI symptom by 31.5% of patients, followed by epigastric pain and regurgitation (22.7% and 13.5% respectively) (table 11).

Table 11. *Dominant upper GI symptom*

	N	%
Heartburn	229	31.5
Epigastric pain	165	22.7
Regurgitation	98	13.5
Belching	87	12.0
Postprandial fullness	62	8.5
Early satiety	27	3.7
Bloating	34	4.7
Nausea	14	1.9
Vomiting	10	1.4
NA	*76*	

Clinical practice on gastroprotection

At the time of the study visit, the majority of study subjects (84.7%) were receiving gastroprotective treatment. Most of them (74.1%) were under PPI-based treatment (table 12).

Table 12. *Gastroprotective treatment*

	N	%
No treatment	**122**	**15.3**
PPI-based therapy	**592**	**74.1**
PPI monotherapy	512	64.1
PPI + Antacid	56	7.0
PPI + H_2RA	20	2.5
PPI + Antacids + H_2RA	4	0.5
Treatment other than PPI	**85**	**10.6**
H_2RA	60	7.5
Antacid	20	2.5
Antacid + H_2RA	5	0.6
NA	*3*	

The intensity of gastroprotection treatment and patients' compliance is depicted in table 13.

Table 13. *Gastroprotective treatment's intensity and compliance*

	PPI		H_2RA		Antacid	
	N	%	N	%	N	%
Treatment Intensity						
Low dose	117	20.6	25	31.3	37	55.2
Standard dose	374	65.8	50	62.5	30	44.8
High dose	77	13.6	5	6.3	0	0
Treatment compliance						
Low compliance	38	7.1	11	14.5	15	24.6
Moderate compliance*	147	27.3	34	44.7	33	54.1
High compliance	354	65.7	31	40.8	13	21.3

* Occasional use

Upper GI symptoms in patient subgroups

The percentages of patients with GERD, dyspepsia and upper GI symptoms receiving no gastroprotection and of those receiving either PPI-based treatment or non-PPI treatment are tabulated in tables 14, 15 & 16 respectively.

Table 14. *Upper GI symptoms in patients receiving no gastroprotection*

	N	%
GERD symptoms	62	51.2
Dyspepsia symptoms	71	58.7
Upper GI symptoms	83	68.0

Table 15. *Upper GI symptoms in patients receiving non-PPI gastroprotection*

	N	%
GERD symptoms	38	50.0
Dyspepsia symptoms	49	65.3
Upper GI symptoms	64	80.0

Table 16. *Upper GI symptoms in patients receiving PPI gastroprotection*

	N	%
GERD symptoms	344	62.2
Dyspepsia symptoms	410	74.0
Upper GI symptoms	473	83.3

The relevant frequencies of GERD, dyspepsia and upper GI symptoms in patients receiving no gastroprotection and receiving either PPI-based treatment or non-PPI treatment are shown in tables 17, 18 & 19 respectively.

Table 17. *Frequency of upper GI symptoms in patients receiving no gastroprotection*

	N	%
GERD symptoms		
No symptoms*	59	48.8
2 days/week	21	17.4
3-5 days/week	38	31.4
6-7 days/week	3	2.5
Dyspepsia symptoms		
No symptoms*	50	41.3
2 days/week	14	11.6
3-5 days/week	52	43.0
6-7 days/week	5	4.1
Upper GI symptoms		
No symptoms*	39	32.0
2 days/week	17	13.9
3-5 days/week	59	48.4
6-7 days/week	7	5.7

* No symptoms or symptoms for 1 day in the last week prior to the study visit

Table 18. *Frequency of upper GI symptoms in patients receiving non-PPI gastroprotection*

	N	%
GERD symptoms		
No symptoms*	38	50.0
2 days/week	13	17.1
3-5 days/week	21	27.6
6-7 days/week	4	5.3
Dyspepsia symptoms		
No symptoms*	26	34.7
2 days/week	12	16.0
3-5 days/week	33	44.0
6-7 days/week	4	5.3
Upper GI symptoms		
No symptoms*	16	20.0
2 days/week	14	17.5
3-5 days/week	44	55.0
6-7 days/week	6	7.5

* No symptoms or symptoms for 1 day in the last week prior to the study visit

Table 19. *Frequency of upper GI symptoms in patients receiving PPI gastroprotection*

	N	%
GERD symptoms		
No symptoms*	209	37.8
2 days/week	89	16.1
3-5 days/week	217	39.2
6-7 days/week	38	6.9
Dyspepsia symptoms		
No symptoms*	144	26.0
2 days/week	90	16.2
3-5 days/week	277	50.0
6-7 days/week	43	7.8
Upper GI symptoms		
No symptoms*	95	16.7
2 days/week	94	16.5
3-5 days/week	314	55.3
6-7 days/week	65	11.4

* No symptoms or symptoms for 1 day in the last week prior to the study visit

The impact of compliance to PPI treatment in upper GI symptoms is depicted in table 20.

Table 20. *Compliance to PPI-based treatment*

	Low compliance		**Moderate compliance***		**High compliance**	
	N	**%**	**N**	**%**	**N**	**%**
GERD symptoms	23	67.6	96	69.6	182	54.8
Dyspepsia symptoms	27	77.1	109	77.9	230	69.5
Upper GI symptoms	32	88.9	125	88.0	266	78.5

*Occasional use

Summary of pharmacokinetic results

Not applicable.

Summary of pharmacodynamic results

Not applicable.

Summary of pharmacogenetic results

Not applicable.

Summary of safety results

Not applicable.