Listing 1 - Adverse events - patient listing

PATIENT NUMBER	AGE	SEX	PERIOD IN STUDY	ADVERSE EVENT (AS CODED)	DOSE	CAT. OF EVENT[a]	DAY[b]	DUR. OF EVENT (DAYS)	INTENSITY[c]	CAUSALITY[d]	COUNTERMEASURES: STUDY DRUG	COUNTERMEASURES: OTHER	OUTCOME
GLIMEPIRIDE + METFORMIN													
101	317	63	M	Db trt	Bronchitis	2	NII	82	7	Moderate	None	No change	Medicament	Subsided
107	1	64	F	Db trt	Hyperlipemia	6	NII	140	-	Moderate	None	No change	Other	Still present
115	6	46	F	Db trt	Urinary tract infection	2	NII	45	10	Moderate	None	No change	Medicament	Subsided
				Db trt	Pyelonephritis	4	EXAC	110	12	Moderate	None	No change	Medicament	Subsided
121	460	69	M	Db trt	Increased appetite	1	EXAC	8	0	Mild	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	1	EXAC	8	0	Mild	Possible	No change	None	Subsided
				Db trt	Increased appetite	1	EXAC	12	0	Mild	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	1	EXAC	12	0	Mild	Possible	No change	None	Subsided
				Db trt	Increased appetite	1	EXAC	20	0	Mild	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	1	EXAC	20	0	Mild	Possible	No change	None	Subsided
				Db trt	Acrodynia	0	NII	110	3	Moderate	None	No change	Other	Subsided
				Db trt	Uveitis	0	NII	123	8	Mild	None	No change	Medicament	Subsided
124	97	50	F	Db trt	Maculopapular rash	2	ADR	76	7	Mild	Possible	No change	Medicament	Subsided
201	21	69	M	Db trt	Bronchitis	4	NII	42	7	Moderate	None	No change	Medicament	Subsided
203	25	45	F	Db trt	Anxiety	2	EXAC	80	19	Moderate	None	No change	Medicament	Subsided
				Db trt	Sweating increased	4	ADR	92	0	Moderate	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	4	ADR	92	0	Moderate	Possible	No change	None	Subsided
				Db trt	Confusion	4	ADR	99	0	Severe	Possible	Perm. discont	Medicament	Subsided
				Db trt	Accidental injury	4	-	99	-	-	-	-	-	-
				Db trt	Urinary tract infection	4	-	99	-	-	-	-	-	-
				Db trt	Hypoglycemia	4	ADR	99	0	Severe	Possible	Perm. discont	Medicament	Subsided
				Db trt	Hypoglycemia	4	ADR	99	0	Severe	Possible	Perm. discont	Medicament	Subsided
205	327	54	M	Db trt	Headache	4	OTH	47	17	Moderate	None	No change	Medicament	Subsided
208	337	65	F	Db trt	Sweating increased	-	ADR	1	0	Moderate	Possible	No change	None	Subsided
				Db trt	Dizziness	-	ADR	1	0	Mild	Possible	No change	None	Subsided
				Db trt	Headache	-	ADR	1	0	Moderate	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	-	ADR	1	0	Moderate	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	-	ADR	1	0	Mild	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	-	ADR	1	0	Moderate	Possible	No change	None	Subsided
				Db trt	Sweating increased	-	ADR	2	0	Mild	Possible	Perm. discont	None	Subsided
				Db trt	Dizziness	-	ADR	2	0	Mild	Possible	Perm. discont	None	Subsided

Note : Shading denotes a serious adverse event

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c Investigator's assessment: mild, moderate, severe

d Investigator's assessment: none, possible

Listing 1 - Adverse events - patient listing

PATIENT NUMBER		AGE	SEX	PERIOD IN STUDY	ADVERSE EVENT (AS CODED)	DOSE	CAT. OF EVENT[a]	DAY[b]	DUR. OF EVENT (DAYS)	INTENSITY[c]	CAUSALITY[d]	COUNTERMEASURES		OUTCOME
												STUDY DRUG	OTHER	
				Db trt	Headache	-	ADR	2	0	Moderate	Possible	Perm. discont	None	Subsided
				Db trt	Hypoglycemia	-	ADR	2	0	Mild	Possible	Perm. discont	None	Subsided
				Db trt	Hypoglycemia	-	ADR	2	0	Mild	Possible	Perm. discont	None	Subsided
				Db trt	Hypoglycemia	-	ADR	2	0	Moderate	Possible	Perm. discont	None	Subsided
209	420	66	M	Db trt	Increased appetite	1	ADR	18	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Asthenia	1	ADR	18	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	18	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	18	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Asthenia	1	ADR	19	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	19	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Increased appetite	1	ADR	42	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Asthenia	1	ADR	42	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	42	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	42	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Tooth disorder	1	OTH	57	7	Moderate	None	No change	Medicament	Subsided
213	306	63	M	Db trt	Malaise	1	ADR	3	0	Moderate	Possible	Dosage reduced	None	Subsided
				Db trt	Tremor	1	ADR	3	0	Moderate	Possible	Dosage reduced	None	Subsided
				Db trt	Increased appetite	1	ADR	3	0	Moderate	Possible	Dosage reduced	None	Subsided
				Db trt	Hypoglycemia	1	ADR	3	0	Moderate	Possible	Dosage reduced	None	Subsided
				Db trt	Hypoglycemia	1	ADR	3	0	Moderate	Possible	Dosage reduced	None	Subsided
				Db trt	Hypoglycemia	1	ADR	3	0	Moderate	Possible	Dosage reduced	None	Subsided
				Db trt	Sweating increased	1	ADR	6	0	Moderate	Possible	Dosage reduced	None	Subsided
				Db trt	Hypoglycemia	1	ADR	6	0	Moderate	Possible	Dosage reduced	None	Subsided
				Db trt	Nervousness	1	ADR	11	0	Moderate	Possible	Dosage reduced	None	Subsided
				Db trt	Hypoglycemia	1	ADR	11	0	Moderate	Possible	Dosage reduced	None	Subsided
				Db trt	Tremor	1	ADR	47	0	Moderate	Possible	Dosage reduced	None	Subsided
				Db trt	Increased appetite	1	ADR	47	0	Moderate	Possible	Dosage reduced	None	Subsided
				Db trt	Hypoglycemia	1	ADR	47	0	Moderate	Possible	Dosage reduced	None	Subsided
				Db trt	Hypoglycemia	1	ADR	47	0	Moderate	Possible	Dosage reduced	None	Subsided
				Db trt	Malaise	1	ADR	48	0	Moderate	Possible	Dosage reduced	None	Subsided
				Db trt	Hypoglycemia	1	ADR	48	0	Moderate	Possible	Dosage reduced	None	Subsided
				Db trt	Sweating increased	1	ADR	62	0	Moderate	Possible	Dosage reduced	None	Subsided
				Db trt	Hypoglycemia	1	ADR	62	0	Moderate	Possible	Dosage reduced	None	Subsided
				Db trt	Psoriasis	0	EXAC	80	49	Mild	None	No change	Medicament	Subsided
				Db trt	Malaise	1	ADR	95	0	Mild	Possible	Dosage reduced	None	Subsided
				Db trt	Hypoglycemia	1	ADR	95	0	Mild	Possible	Dosage reduced	None	Subsided
				Db trt	Nervousness	1	ADR	96	0	Mild	Possible	Dosage reduced	None	Subsided
				Db trt	Sweating increased	1	ADR	96	0	Mild	Possible	Dosage reduced	None	Subsided
				Db trt	Hypoglycemia	1	ADR	96	0	Mild	Possible	Dosage reduced	None	Subsided
				Db trt	Hypoglycemia	1	ADR	96	0	Mild	Possible	Dosage reduced	None	Subsided

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Listing 1 - Adverse events - patient listing

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											STUDY DRUG	OTHER	
[illegible]			Db trt	Infection [illegible]	[illegible]	EXAC	18	10	[illegible] Severe	None	No change	Medicament [illegible]	Subsided
305	32	52	F	Db trt	Malaise	4	ADR	44	0	Moderate	Possible	No change	None	Subsided
				Db trt	Sweating increased	4	ADR	44	0	Moderate	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	4	ADR	44	0	Moderate	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	4	ADR	44	0	Moderate	Possible	No change	None	Subsided
316	27	56	M	Db trt	Headache	4	ADR	3	0	Mild	None	No change	Medicament	Subsided
				Db trt	Depression	4	EXAC	64	27	Moderate	None	No change	Medicament	Subsided
				Db trt	Malaise	4	ADR	90	0	Moderate	Possible	Dosage reduced	Other	Subsided
				Db trt	Hypoglycemia	4	ADR	90	0	Moderate	Possible	Dosage reduced	Other	Subsided
				Db trt	Increased appetite	4	ADR	118	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	4	ADR	118	0	Mild	Possible	No change	Other	Subsided
				Db trt	Increased appetite	4	ADR	119	0	Moderate	Possible	Dosage reduced	Other	Subsided
				Db trt	Hypoglycemia	4	ADR	119	0	Moderate	Possible	Dosage reduced	Other	Subsided
				Db trt	Hypoglycemia	4	ADR	129	0	Mild	Possible	No change	None	Subsided
506	42	55	M	Db trt	Gastroenteritis	2	NII	34	1	Mild	Possible	No change	Medicament	Subsided
				Db trt	Tendon disorder	2	EXAC	42	-	Moderate	None	No change	Medicament	Still present
701	251	70	F	Db trt	Rhinitis	1	NII	4	20	Mild	None	No change	Medicament	Subsided
				Db trt	Paresthesia	2	ADR	57	49	Mild	Possible	No change	Medicament	Subsided
701	253	63	M	Db trt	Dizziness	1	ADR	1	0	Mild	Possible	No change	Other	Subsided
				Db trt	Malaise	1	ADR	1	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	1	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	1	0	Mild	Possible	No change	Other	Subsided
				Db trt	Dizziness	1	NII	57	1	Moderate	None	No change	None	Subsided
701	258	57	M	Db trt	Diarrhea	1	ADR	72	163	Moderate	Possible	No change	Medicament	Subsided
				Db trt	Dizziness	1	ADR	131	20	Moderate	Possible	No change	Medicament	Subsided
801	442	62	M	Db trt	Sweating increased	0	ADR	13	0	Moderate	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	0	ADR	13	0	Moderate	Possible	No change	None	Subsided
				Db trt	Sweating increased	0	ADR	14	0	Moderate	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	0	ADR	14	0	Moderate	Possible	No change	None	Subsided
				Db trt	Sweating increased	0	ADR	44	0	Moderate	Possible	No change	Medicament	Subsided
				Db trt	Hypoglycemia	0	ADR	44	0	Moderate	Possible	No change	Medicament	Subsided
				Db trt	Sweating increased	0	ADR	45	0	Moderate	Possible	No change	Medicament	Subsided
				Db trt	Hypoglycemia	0	ADR	45	0	Moderate	Possible	No change	Medicament	Subsided

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												STUDY DRUG	OTHER	
				Db trt	Sweating increased	0	ADR	62	0	Moderate	Possible	No change	Medicament	Subsided
				Db trt	Hypoglycemia	0	ADR	62	0	Moderate	Possible	No change	Medicament	Subsided
				Db trt	Sweating increased	0	ADR	89	0	Moderate	Possible	No change	Medicament	Subsided
				Db trt	Hypoglycemia	0	ADR	89	0	Moderate	Possible	No change	Medicament	Subsided
				Db trt	Sweating increased	0	ADR	96	0	Moderate	Possible	No change	Medicament	Subsided
				Db trt	Hypoglycemia	0	ADR	96	0	Moderate	Possible	No change	Medicament	Subsided
				Db trt	Sweating increased	0	ADR	98	4	Moderate	Possible	Perm. discont	None	Subsided
				Db trt	Hypoglycemia	0	ADR	98	4	Moderate	Possible	Perm. discont	None	Subsided
				Db trt	Sweating increased	0	ADR	119	0	Moderate	Possible	Perm. discont	None	Subsided
				Db trt	Hypoglycemia	0	ADR	119	0	Moderate	Possible	Perm. discont	None	Subsided
				Db trt	Sweating increased	0	ADR	127	0	Moderate	Possible	Perm. discont	None	Subsided
				Db trt	Hypoglycemia	0	ADR	127	0	Moderate	Possible	Perm. discont	None	Subsided
				Db trt	Sweating increased	0	ADR	135	0	Moderate	Possible	Perm. discont	None	Subsided
				Db trt	Hypoglycemia	0	ADR	135	0	Moderate	Possible	Perm. discont	None	Subsided
810	182	55	F	Db trt	Gastritis	1	NII	36	11	Severe	Possible	No change	Medicament	Subsided
				Db trt	Gastritis	4	NII	78	7	Moderate	None	No change	Medicament	Subsided
				Db trt	Anal pain	6	NII	140	-	Moderate	None	No change	Medicament	Still present
812	406	66	F	Db trt	Flu syndrome	4	NII	58	4	Mild	None	No change	Medicament	Subsided
				Db trt	Sweating increased	6	ADR	72	0	Mild	Possible	No change	Other	Subsided
				Db trt	Tremor	6	ADR	72	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	6	ADR	72	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	6	ADR	72	0	Mild	Possible	No change	Other	Subsided
818	444	46	M	Db trt	Tremor	2	ADR	21	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	2	ADR	21	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Sweating increased	2	ADR	22	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	2	ADR	22	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Increased appetite	2	ADR	24	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	2	ADR	24	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Increased appetite	2	ADR	37	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	2	ADR	37	0	Moderate	Possible	No change	Other	Subsided
[illegible]		[illegible]	[illegible]	Db trt	Fever	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]		[illegible]	[illegible]	Db trt	Hemorrhoids	[illegible]	[illegible]	12	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	EXAC	12	[illegible]	[illegible]	[illegible]	Perm. discont	[illegible]	[illegible]
[illegible]		[illegible]	[illegible]	After	Large intestine perforation	[illegible]	EXAC	[illegible]	144	Severe	None	[illegible]	Other	[illegible]
901	393	41	M	Db trt	Kidney pain	1	EXAC	82	3	Moderate	None	No change	Medicament	Subsided

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											STUDY DRUG	OTHER	
902	351	60	M	Db trt	Pharyngitis	1	NII	16	2	Mild	None	No change	None	Subsided
				Db trt	Epistaxis	1	NII	16	1	Mild	None	No change	None	Subsided
				Db trt	Epistaxis	6	NII	82	3	Mild	None	No change	Medicament	Subsided
905	229	60	F	Db trt	Hypoglycemia	4	ADR	46	0	Mild	Possible	Dosage reduced	Other	Subsided
				Db trt	Hypoglycemia	4	ADR	47	0	Mild	Possible	Dosage reduced	Other	Subsided
				Db trt	Hypoglycemia	2	NII	97	0	Mild	Possible	Dosage reduced	Other	Subsided
909	222	62	M	Db trt	Hypoglycemia	2	ADR	29	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	52	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	52	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	54	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	55	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	55	0	Mild	Possible	No change	Other	Subsided
				Db trt	Abnormal stools	0	NII	77	2	Mild	None	No change	None	Subsided
				Db trt	Hypoglycemia	1	ADR	85	0	Mild	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	1	ADR	88	0	Mild	Possible	No change	Other	Subsided
				Db trt	Back pain	1	NII	91	10	Mild	None	No change	Medicament	Subsided
				Db trt	Hypoglycemia	1	ADR	92	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	115	0	Mild	Possible	No change	Other	Subsided
909	350	50	F	Db trt	Nausea	2	NII	28	4	Mild	Possible	Dosage reduced	None	Subsided
				Db trt	Hypoglycemia	6	ADR	117	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	6	ADR	127	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	6	ADR	132	0	Mild	Possible	No change	Other	Subsided
910	392	56	M	Db trt	Constipation	1	NII	47	2	Mild	None	No change	Other	Subsided
1007	211	45	M	Db trt	Rhinitis	4	NII	64	5	Moderate	None	No change	Medicament	Subsided
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
			After	Left heart failure	-	NII	41	51	Moderate	None		Medicament	Subsided
1101	172	47	M	Db trt	Impotence	1	ADR	12	131	Moderate	Possible	No change	None	Subsided
				Db trt	Pharyngitis	2	NII	27	31	Mild	None	No change	Medicament	Subsided
1103	104	48	M	Db trt	Vomiting	1	NII	6	113	Mild	None	No change	Medicament	Subsided
				Db trt	Bronchitis	1	NII	12	13	Moderate	None	No change	Medicament	Subsided
				Db trt	Psoriasis	1	ADR	33	-	Mild	Possible	No change	None	Still present
1103	166	66	F	Db trt	Nausea	1	ADR	12	62	Mild	Possible	No change	Medicament	Subsided
				Db trt	Diarrhea	1	ADR	12	-	Mild	Possible	No change	Medicament	Still present

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[illegible]			Db trt	Palpitation	1	NII	86	-	Severe	None	Temp. discont.	Both	Subsided
			Db trt	Atrial fibrillation	1	NII	86	-	Severe	None	Temp. discont.	Both	Subsided
			Db trt	Tachycardia	1	NII	86	-	Severe	None	Temp. discont.	Both	Subsided
			Db trt	Malaise	1	NII	86	-	Severe	None	Temp. discont.	Both	Subsided
			Db trt	Anxiety	1	NII	126	-	Moderate	None	No change	Medicament	Still present
			Db trt	Sweating increased	1	NII	126	-	Moderate	None	No change	Medicament	Still present
			Db trt	Palpitation	1	NII	126	-	Moderate	None	No change	Medicament	Still present
			Db trt	Tremor	1	NII	126	-	Moderate	None	No change	Medicament	Still present
			Db trt	Headache	1	NII	126	-	Moderate	None	No change	Medicament	Still present
1103	169	70	M	Db trt	Bronchitis	1	NII	85	-	Mild	None	No change	Medicament	Still present
1209	264	69	M	Db trt	Accidental injury	1	EXAC	122	0	Mild	None	No change	Other	Subsided
1209	266	53	M	Db trt	Sweating increased	4	ADR	76	0	Mild	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	4	ADR	76	0	Mild	Possible	No change	None	Subsided
				Db trt	Malaise	4	ADR	77	0	Mild	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	4	ADR	77	0	Mild	Possible	No change	None	Subsided
1303	149	70	M	Db trt	Pelvic pain	1	NII	74	7	Mild	None	No change	Medicament	Subsided
1311	147	52	M	Db trt	Tremor	1	ADR	8	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	8	0	Mild	Possible	No change	Other	Subsided

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c Investigator's assessment: mild, moderate, severe

d Investigator's assessment: none, possible

Listing 1 - Adverse events - patient listing

PATIENT NUMBER	AGE	SEX	PERIOD IN STUDY	ADVERSE EVENT (AS CODED)	DOSE	CAT. OF EVENT[a]	DAY[b]	DUR. OF EVENT (DAYS)	INTEN-SITY[c]	CAUSA-LITY[d]	COUNTERMEASURES		OUTCOME
											STUDY DRUG	OTHER	
1315	151	56	M	Db trt Pharyngitis	4	NII	138	3	Mild	None	No change	Medicament	Subsided
1505	242	59	M	Db trt Malaise	1	ADR	24	0	Moderate	None	No change	None	Subsided
				Db trt Hypoglycemia	1	ADR	24	0	Moderate	None	No change	None	Subsided
				Db trt Malaise	1	ADR	25	0	Moderate	None	No change	None	Subsided
				Db trt Hypoglycemia	1	ADR	25	0	Moderate	None	No change	None	Subsided
				Db trt Malaise	0	ADR	28	0	Moderate	None	Temp. discont	None	Subsided
				Db trt Hypoglycemia	0	ADR	28	0	Moderate	None	Temp. discont	None	Subsided
				Db trt Malaise	1	ADR	56	0	Moderate	None	No change	None	Subsided
				Db trt Hypoglycemia	1	ADR	56	0	Moderate	None	No change	None	Subsided
1604	163	49	F	Db trt Diarrhea	1	ADR	2	63	Moderate	Possible	No change	None	Subsided
1611	338	46	M	Db trt Malaise	2	ADR	22	0	Mild	Possible	Dosage reduced	None	Subsided
				Db trt Hypoglycemia	2	ADR	22	0	Mild	Possible	Dosage reduced	None	Subsided
				Db trt Sweating increased	1	ADR	73	0	Mild	Possible	Dosage reduced	None	Subsided
				Db trt Increased appetite	1	ADR	73	0	Mild	Possible	Dosage reduced	None	Subsided
				Db trt Malaise	1	ADR	73	0	Mild	Possible	Dosage reduced	None	Subsided
				Db trt Hypoglycemia	1	ADR	73	0	Mild	Possible	Dosage reduced	None	Subsided
				Db trt Hypoglycemia	1	ADR	73	0	Mild	Possible	Dosage reduced	None	Subsided
				Db trt Hypoglycemia	1	ADR	73	0	Mild	Possible	Dosage reduced	None	Subsided
				Db trt Malaise	1	ADR	75	0	Mild	Possible	No change	None	Subsided
				Db trt Increased appetite	1	ADR	75	0	Mild	Possible	No change	None	Subsided
				Db trt Sweating increased	1	ADR	75	0	Mild	Possible	No change	None	Subsided
				Db trt Hypoglycemia	1	ADR	75	0	Mild	Possible	No change	None	Subsided
				Db trt Hypoglycemia	1	ADR	75	0	Mild	Possible	No change	None	Subsided
				Db trt Hypoglycemia	1	ADR	75	0	Mild	Possible	No change	None	Subsided
				Db trt Amnesia	1	NII	132	-	Mild	None	No change	Medicament	Still present
1701	237	51	M	Db trt Asthenia	6	NII	64	30	Mild	None	No change	None	Subsided
				Db trt Thorax pain	6	NII	150	35	Mild	None	No change	None	Subsided
1701	328	51	F	Db trt Arthrosis	6	EXAC	64	20	Mild	None	No change	None	Subsided
				Db trt Hyperlipemia	6	NII	131	-	Mild	None	No change	None	Still present
1703	234	67	M	Db trt Diarrhea	1	ADR	17	85	Mild	Possible	No change	None	Subsided
				Db trt Paresthesia	6	NII	93	61	Moderate	None	No change	Medicament	Subsided
				Db trt Pruritus	6	NII	97	77	Moderate	None	No change	Medicament	Subsided
1703	407	69	M	Db trt Gastrointestinal disorder	6	EXAC	82	75	Moderate	Possible	No change	Medicament	Subsided

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d Investigator's assessment: none, possible

Listing 1 - Adverse events - patient listing

PATIENT NUMBER	AGE	SEX	PERIOD IN STUDY	ADVERSE EVENT (AS CODED)	DOSE	CAT. OF EVENT[a]	DAY[b]	DUR. OF EVENT (DAYS)	INTENSITY[c]	CAUSALITY[d]	COUNTERMEASURES		OUTCOME
											STUDY DRUG	OTHER	
1710	412	57	F	Db trt	Hyperlipemia	-	NII	-2	232	Mild	None	No change	None	Subsided
1713	272	62	M	Db trt	Sweating increased	-	ADR	2	0	Severe	Possible	Perm. discont	Other	Subsided
				Db trt	Increased appetite	-	ADR	2	0	Severe	Possible	Perm. discont	Other	Subsided
				Db trt	Malaise	-	ADR	2	0	Severe	Possible	Perm. discont	Other	Subsided
				Db trt	Hypoglycemia	-	ADR	2	0	Severe	Possible	Perm. discont	Other	Subsided
				Db trt	Hypoglycemia	-	ADR	2	0	Severe	Possible	Perm. discont	Other	Subsided
				Db trt	Hypoglycemia	-	ADR	2	0	Severe	Possible	Perm. discont	Other	Subsided
1715	236	45	M	Db trt	Asthenia	2	ADR	43	0	Mild	Possible	No change	Other	Subsided
				Db trt	Sweating increased	2	ADR	43	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	2	ADR	43	0	Mild	Possible	No change	Other	Subsided
1803	203	63	F	Db trt	Rhinitis	2	NII	117	8	Mild	None	No change	Medicament	Subsided
				Db trt	Cough increased	2	NII	117	8	Mild	None	No change	Medicament	Subsided
1806	207	53	M	Db trt	Rhinitis	2	NII	25	36	Mild	None	No change	Medicament	Subsided
				Db trt	Bone fracture (not spontaneous)	2	OTH	110	43	Moderate	None	No change	Other	Residual effect
[illegible]	210	[illegible]	[illegible]	Db trt	Nodal tachycardia	[illegible]	OTH	59	[illegible]	Severe	None	No change	Medicament	Subsided
				Db trt	Nodal tachycardia		OTH	59	2 1	Severe	None	No change	Medicament	Subsided
[illegible]	461	[illegible]	[illegible]	Db trt	[illegible]	[illegible]	OTH	82	[illegible]	Severe	None	No change	Medicament	Subsided
1816	455	46	M	Db trt	Cough increased	4	NII	42	11	Moderate	None	No change	Medicament	Subsided
				Db trt	Myalgia	6	NII	84	38	Mild	None	No change	Medicament	Subsided
1901	283	58	M	Db trt	Arthralgia	6	NII	71	74	Moderate	None	No change	Both	Subsided
				Db trt	Flu syndrome	6	NII	132	9	Mild	None	No change	Medicament	Subsided
5201	113	60	M	Db trt	Sweating increased	2	ADR	71	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	2	ADR	71	0	Mild	Possible	No change	Other	Subsided
				Db trt	Sweating increased	2	ADR	86	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	2	ADR	86	0	Mild	Possible	No change	Other	Subsided
				Db trt	Sweating increased	2	ADR	88	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	2	ADR	88	0	Mild	Possible	No change	Other	Subsided
5201	277	54	F	Db trt	Sweating increased	2	ADR	28	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Palpitation	2	ADR	28	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	2	ADR	28	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	2	ADR	28	0	Mild	Possible	No change	Other	Subsided
				Db trt	Tremor	6	ADR	85	0	Moderate	Possible	No change	Other	Subsided

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Listing 1 - Adverse events - patient listing

PATIENT NUMBER		AGE	SEX	PERIOD IN STUDY	ADVERSE EVENT (AS CODED)	DOSE	CAT. OF EVENT[a]	DAY[b]	DUR. OF EVENT (DAYS)	INTEN-SITY[c]	CAUSA-LITY[d]	COUNTERMEASURES		OUTCOME
												STUDY DRUG	OTHER	
				Db trt	Asthenia	6	ADR	85	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	6	ADR	85	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	6	ADR	85	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Tremor	6	ADR	120	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Asthenia	6	ADR	120	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	6	ADR	120	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	6	ADR	120	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	6	ADR	120	0	Moderate	Possible	No change	Other	Subsided
5201	278	46	F	Db trt	Asthenia	1	NII	113	-	Moderate	Possible	No change	None	Still present
				Db trt	Fever	1	NII	131	8	Moderate	None	No change	Medicament	Subsided
				Db trt	Tremor	1	NII	138	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	NII	138	0	Moderate	Possible	No change	Other	Subsided
5401	78	36	F	Db trt	Sweating increased	1	ADR	141	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	141	0	Moderate	Possible	No change	Other	Subsided
5501	192	36	M	Db trt	Pallor	1	ADR	4	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Tremor	1	ADR	4	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Sweating increased	1	ADR	4	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	4	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	4	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	4	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Pallor	1	ADR	11	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Tremor	1	ADR	11	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Sweating increased	1	ADR	11	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	11	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	11	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	11	0	Moderate	Possible	No change	Other	Subsided
5501	193	59	F	Db trt	Asthenia	1	ADR	4	0	Severe	Possible	Dosage reduced	Other	Subsided
				Db trt	Sweating increased	1	ADR	4	0	Severe	Possible	Dosage reduced	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	4	0	Severe	Possible	Dosage reduced	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	4	0	Severe	Possible	Dosage reduced	Other	Subsided
				Db trt	Asthenia	1	ADR	10	0	Severe	Possible	Dosage reduced	Other	Subsided
				Db trt	Sweating increased	1	ADR	10	0	Severe	Possible	Dosage reduced	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	10	0	Severe	Possible	Dosage reduced	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	10	0	Severe	Possible	Dosage reduced	Other	Subsided
				Db trt	Headache	0	ADR	21	21	Mild	Possible	Dosage reduced	None	Subsided
				Db trt	Asthenia	2	ADR	81	0	Moderate	Possible	Dosage reduced	Other	Subsided
				Db trt	Sweating increased	2	ADR	81	0	Moderate	Possible	Dosage reduced	Other	Subsided
				Db trt	Hypoglycemia	2	ADR	81	0	Moderate	Possible	Dosage reduced	Other	Subsided

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											STUDY DRUG	OTHER	
			Db trt	Hypoglycemia	2	ADR	81	0	Moderate	Possible	Dosage reduced	Other	Subsided
5501	473	67	M	Db trt	Malaise	1	ADR	8	0	Mild	Possible	Temp. discont	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	8	0	Mild	Possible	Temp. discont	Other	Subsided
				Db trt	Flu syndrome	2	NII	73	18	Moderate	None	No change	Medicament	Subsided
				Db trt	Hypoglycemia	2	ADR	113	0	Moderate	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	2	ADR	120	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	2	ADR	127	0	Mild	Possible	No change	Other	Subsided
5801	61	68	F	Db trt	Body odor	1	ADR	1	150	Mild	Possible	No change	None	Died
				Db trt	Dyspepsia	2	NII	76	75	Severe	None	Perm. discont	None	Died
				Db trt	Gastritis	2	NII	94	57	Severe	None	Perm. discont	None	Died
				After [illegible]	[illegible]	2	OTH	423	20	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
				After [illegible]	Cardiac [illegible]	2	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
				After [illegible]	Ascites	2	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
5901	83	50	F	Db trt	Hypoglycemia	4	EXAC	55	0	Mild	Possible	No change	Other	Subsided
6201	67	53	F	Db trt	Sweating increased	2	ADR	23	0	Mild	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	2	ADR	23	0	Mild	Possible	No change	None	Subsided
				Db trt	Increased appetite	2	ADR	24	0	Mild	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	2	ADR	24	0	Mild	Possible	No change	None	Subsided
				Db trt	Headache	2	ADR	25	0	Mild	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	2	ADR	25	0	Mild	Possible	No change	None	Subsided
				Db trt	Gastroenteritis	2	NII	66	3	Moderate	None	No change	Medicament	Subsided
				Db trt	Herpes simplex	2	NII	70	5	Severe	None	No change	Medicament	Subsided
				Db trt	Bronchitis	2	NII	82	4	Moderate	None	No change	Medicament	Subsided
				Db trt	Back pain	4	NII	128	4	Moderate	None	No change	Medicament	Subsided
				Db trt	Hypoglycemia	4	ADR	129	0	Mild	Possible	No change	None	Subsided
6401	92	54	M	Db trt	Increased appetite	4	ADR	42	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	4	ADR	42	0	Mild	Possible	No change	Other	Subsided
				Db trt	Increased appetite	4	ADR	46	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	4	ADR	46	0	Mild	Possible	No change	Other	Subsided
				Db trt	Increased appetite	4	ADR	58	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	4	ADR	58	0	Mild	Possible	No change	Other	Subsided
				Db trt	Back pain	6	NII	105	30	Mild	None	No change	Medicament	Subsided
6401	94	49	F	Db trt	Hypoglycemia	1	ADR	16	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	17	0	Mild	Possible	No change	Other	Subsided
				Db trt	Tendon disorder	1	NII	79	7	Mild	None	No change	Medicament	Subsided

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											STUDY DRUG	OTHER	
6701	130	63	M	Db trt Hypoglycemia	1	ADR	62	0	Mild	Possible	No change	Other	Subsided
				Db trt Sweating increased	2	ADR	118	0	Mild	Possible	No change	Other	Subsided
				Db trt Hypoglycemia	2	ADR	118	0	Mild	Possible	No change	Other	Subsided
6701	434	48	M	Db trt Tremor	2	ADR	26	0	Mild	Possible	No change	None	Subsided
				Db trt Increased appetite	2	-	26	0	Mild	Possible	No change	None	Subsided
				Db trt Hypoglycemia	2	ADR	26	0	Mild	Possible	No change	None	Subsided
				Db trt Hypoglycemia	2	-	26	0	Mild	Possible	No change	None	Subsided
				Db trt Malaise	2	ADR	77	0	Mild	Possible	No change	None	Subsided
				Db trt Malaise	2	ADR	77	0	Mild	Possible	No change	Other	Subsided
				Db trt Hypoglycemia	2	ADR	77	0	Mild	Possible	No change	Other	Subsided
				Db trt Hypoglycemia	2	ADR	77	0	Mild	Possible	No change	Other	Subsided
				Db trt Malaise	2	ADR	78	0	Mild	Possible	No change	Other	Subsided
				Db trt Hypoglycemia	2	ADR	78	0	Mild	Possible	No change	Other	Subsided
				Db trt Malaise	2	ADR	80	0	Mild	Possible	No change	Other	Subsided
				Db trt Hypoglycemia	2	ADR	80	0	Mild	Possible	No change	Other	Subsided
				Db trt Malaise	2	ADR	82	0	Mild	Possible	No change	Other	Subsided
				Db trt Hypoglycemia	2	ADR	82	0	Mild	Possible	No change	Other	Subsided
6801	56	60	M	Db trt Tendon disorder	2	EXAC	31	20	Moderate	None	No change	Medicament	Subsided
				Db trt Rhinitis	2	NII	36	5	Mild	None	No change	Medicament	Subsided
				Db trt Diarrhea	6	NII	127	4	Mild	None	No change	None	Subsided
7001	198	65	F	Db trt Rhinitis	6	NII	76	8	Mild	None	No change	Medicament	Subsided
7201	120	63	M	Db trt Impotence	1	ADR	37	-	Moderate	Possible	No change	None	Still present

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											STUDY DRUG	OTHER	
METFORMIN													
101	318	64	F	Db trt	Back pain	1	EXAC	7	11	Severe	None	No change	Medicament	Subsided
				Db trt	Diarrhea	6	ADR	78	-	Moderate	Possible	No change	Medicament	Still present
107	8	69	F	Db trt	Hyperlipemia	6	NII	140	-	Moderate	Possible	No change	Other	Still present
110	330	61	M	Db trt	Increased appetite	2	EXAC	16	0	Mild	Possible	Temp. discont	None	Subsided
				Db trt	Hypoglycemia	-	EXAC	16	0	Mild	Possible	Temp. discont	None	Subsided
				Db trt	Tremor	-	EXAC	22	0	Moderate	Possible	Temp. discont	None	Subsided
				Db trt	Increased appetite	-	EXAC	22	0	Severe	Possible	Temp. discont	None	Subsided
				Db trt	Palpitation	-	EXAC	22	0	Mild	Possible	Temp. discont	None	Subsided
				Db trt	Hypoglycemia	-	EXAC	22	0	Moderate	Possible	Temp. discont	None	Subsided
				Db trt	Hypoglycemia	-	EXAC	22	0	Severe	Possible	Temp. discont	None	Subsided
212	12	58	M	Db trt	Sweating increased	1	ADR	7	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	7	0	Mild	Possible	No change	Other	Subsided
				Db trt	Diarrhea	1	ADR	12	-	Moderate	Possible	No change	Medicament	Still present
				Db trt	Urticaria	1	OTH	16	13	Moderate	Possible	No change	Medicament	Subsided
				Db trt	Malaise	0	ADR	19	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	0	ADR	19	0	Mild	Possible	No change	Other	Subsided
				Db trt	Increased appetite	1	ADR	58	0	Mild	Possible	No change	Other	Subsided
				Db trt	Hypoglycemia	1	ADR	58	0	Mild	Possible	No change	Other	Subsided
214	307	61	F	Db trt	Diarrhea	4	ADR	83	8	Moderate	Possible	No change	Medicament	Subsided
				Db trt	SGOT increased	6	ADR	141	-	Moderate	Possible	No change	None	Still present
				Db trt	Hyperlipemia	6	EXAC	141	-	Severe	None	No change	Medicament	Still present
304	370	49	M	Db trt	Back pain	-	NII	-2	7	Mild	None	No change	Medicament	Subsided
				Db trt	Edema	1	OTH	4	-	Mild	None	No change	None	Still present
				Db trt	Tendon disorder	6	OTH	75	10	Mild	None	No change	Medicament	Subsided
				Db trt	Pruritus	6	ADR	75	-	Moderate	None	No change	Medicament	Still present
				Db trt	Tendon disorder	6	EXAC	136	-	Moderate	None	No change	Medicament	Still present
				Db trt	Eczema	6	OTH	141	-	Moderate	Possible	No change	Medicament	Still present
309	30	44	M	Db trt	Bronchitis	1	NII	7	8	Moderate	None	No change	Medicament	Subsided
316	35	60	M	Db trt	Anorexia	4	ADR	51	-	Mild	Possible	No change	None	Still present
				Db trt	Bradycardia	6	EXAC	108	1	Moderate	Possible	No change	Medicament	Subsided
				Db trt	Hypotension	6	ADR	108	41	Mild	Possible	No change	Medicament	Subsided

Note : Shading denotes a serious adverse event

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b First day of study medication=day 1. Day before Day 1=Day-1, i.e.there is no Day 0.

c Investigator's assessment: mild, moderate, severe

d Investigator's assessment: none, possible

Listing 1 - Adverse events - patient listing

PATIENT NUMBER		AGE	SEX	PERIOD IN STUDY	ADVERSE EVENT (AS CODED)	DOSE	CAT. OF EVENT[a]	DAY[b]	DUR. OF EVENT (DAYS)	INTEN-SITY[c]	CAUSA-LITY[d]	COUNTERMEASURES		OUTCOME
												STUDY DRUG	OTHER	
503	305	64	F	Db trt	Diarrhea	-	ADR	-3	40	Mild	Possible	No change	None	Subsided
701	256	50	F	Db trt	Neck pain	1	NII	16	4	Mild	None	No change	None	Subsided
				Db trt	Hot flashes	2	NII	27	27	Moderate	None	No change	Medicament	Subsided
				Db trt	Neurosis	2	NII	38	12	Mild	Possible	No change	None	Subsided
				Db trt	Asthenia	2	ADR	46	0	Moderate	Possible	No change	None	Subsided
				Db trt	Dry mouth	2	ADR	46	0	Mild	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	2	ADR	46	0	Moderate	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	2	ADR	46	0	Mild	Possible	No change	None	Subsided
				Db trt	Arthralgia	2	NII	106	3	Moderate	None	No change	Medicament	Subsided
[illegible]														
808	90	49	F	Db trt	Sweating increased	4	OTH	60	0	Moderate	None	No change	None	Subsided
				Db trt	Hypoglycemia	4	OTH	60	0	Moderate	None	No change	None	Subsided
810	389	65	M	Db trt	Arthralgia	4	NII	57	22	Moderate	None	No change	Medicament	Subsided
[illegible]														
				Db trt	Arthralgia	6	EXAC	128	11	Moderate	None	No change	Medicament	Subsided
812	409	61	M	Db trt	Muscle cramps	2	NII	21	39	Mild	None	No change	Medicament	Subsided
816	186	67	M	Db trt	Increased appetite	2	ADR	14	0	Mild	Possible	Dosage reduced	Other	Subsided
				Db trt	Hypoglycemia	-	ADR	14	0	Mild	Possible	Dosage reduced	Other	Subsided
				Db trt	Hyperglycemia	-	EXAC	54	145	Severe	None	Perm. discont	Medicament	Subsided
902	417	47	M	Db trt	Hyperglycemia	1	OTH	28	156	Severe	Possible	Perm. discont	Medicament	Subsided
				Db trt	Diarrhea	2	NII	42	0	Moderate	None	No change	None	Subsided
903	226	65	M	Db trt	Bronchitis	4	NII	40	7	Mild	None	No change	Medicament	Subsided
				Db trt	Weight loss	-	OTH	42	-	Moderate	Possible	Perm. discont	Medicament	Still present
905	375	58	M	Db trt	Rhinitis	6	NII	97	4	Mild	None	No change	Medicament	Subsided
				Db trt	Arthrosis	6	NII	118	4	Moderate	None	No change	Medicament	Subsided
1011	452	53	M	Db trt	Bronchitis	4	NII	55	6	Moderate	None	No change	Medicament	Subsided
1015	216	58	F	Db trt	Cough increased	4	NII	58	30	Mild	None	No change	Medicament	Subsided

Note : Shading denotes a serious adverse event

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d Investigator's assessment: none, possible

Listing 1 - Adverse events - patient listing

PATIENT NUMBER	AGE	SEX	PERIOD IN STUDY	ADVERSE EVENT (AS CODED)	DOSE	CAT. OF EVENT[a]	DAY[b]	DUR. OF EVENT (DAYS)	INTEN-SITY[c]	CAUSA-LITY[d]	COUNTERMEASURES		OUTCOME
											STUDY DRUG	OTHER	
1022	64	M	Db trt	Asthenia	1	OTH	16	76	Mild	None	No change	None	Subsided
			Db trt	Cyst	2	NII	42	7	Mild	None	No change	Both	Subsided
1101	58	M	Db trt	Hypoglycemia	2	ADR	29	0	Mild	Possible	No change	None	Subsided
			Db trt	Hypoglycemia	2	ADR	30	0	Mild	Possible	No change	None	Subsided
1102	66	M	Db trt	Sweating increased	4	ADR	67	0	Moderate	Possible	No change	Other	Subsided
			Db trt	Malaise	4	ADR	67	0	Moderate	Possible	No change	Other	Subsided
			Db trt	Hypoglycemia	4	ADR	67	0	Moderate	Possible	No change	Other	Subsided
			Db trt	Hypoglycemia	4	ADR	67	0	Moderate	Possible	No change	Other	Subsided
[illegible]			Db trt	[illegible]	6	EXAC	26	24	[illegible]	None	No change	Both	Resolved with effect
[illegible]			Db trt	[illegible]	8	EXAC	135	[illegible]	Severe	[illegible]	[illegible]	Both	Subsided
1502	68	F	Db trt	Anemia	-	NII	-3	13	Moderate	None	No change	None	Subsided
			Db trt	Pharyngitis	-	NII	-1	3	Moderate	None	No change	None	Subsided
			Db trt	Colitis	2	NII	27	-	Moderate	None	No change	None	Still present
[illegible]	[illegible]	[illegible]	Db trt	Weight loss	-	NII	3	-	[illegible]	None	No change	Both	Still present
[illegible]	[illegible]	[illegible]	Db trt	[illegible] of mouth	-	NII	15	-	Moderate	None	No change	None	Still present
			Db trt	Gastritis	-	NII	32	-	Moderate	Possible	No change	None	-
[illegible]	[illegible]	[illegible]	Db trt	Dysphagia	-	NII	44	-	[illegible]	[illegible]	[illegible]	[illegible]	Still present
[illegible]	[illegible]	[illegible]	Db trt	Asthenia	-	NII	[illegible]	-	Severe	[illegible]	[illegible]	[illegible]	Still present
1611	51	M	Db trt	Nausea	6	ADR	69	2	Mild	Possible	Dosage reduced	None	Subsided
			Db trt	Malaise	6	ADR	69	2	Mild	Possible	Dosage reduced	None	Subsided
			Db trt	Hypoglycemia	6	ADR	69	2	Mild	Possible	Dosage reduced	None	Subsided
			Db trt	Hypoglycemia	6	ADR	69	2	Mild	Possible	Dosage reduced	None	Subsided
1701	50	F	Db trt	Neuralgia	4	NII	58	27	Moderate	None	No change	Both	Subsided
			Db trt	Weight gain	6	EXAC	117	-	Moderate	None	No change	None	Still present
1703	68	F	Db trt	Diarrhea	2	ADR	25	57	Moderate	Possible	No change	Medicament	Subsided
			Db trt	Phlebitis	6	NII	66	5	Mild	None	No change	Medicament	Subsided
1703	69	F	Db trt	Arthrosis	4	EXAC	47	6	Mild	None	No change	Medicament	Subsided
1716	59	F	Db trt	Sinusitis	2	NII	30	13	Moderate	None	No change	Medicament	Subsided
[illegible]	[illegible]	[illegible]	Db trt	[illegible] disorder	[illegible]	EXAC	[illegible]	[illegible]	[illegible]	None	[illegible]	Other	Subsided
[illegible]	[illegible]	[illegible]	Db trt	[illegible]	[illegible]	[illegible]	26	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	Db trt	Urinary incontinence	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Note : Shading denotes a serious adverse event
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b First day of study medication=day 1. Day before Day 1=Day-1, i.e.there is no Day 0.
c Investigator's assessment: mild, moderate, severe
d Investigator's assessment: none, possible

Listing 1 - Adverse events - patient listing

PATIENT NUMBER	AGE	SEX	PERIOD IN STUDY	ADVERSE EVENT (AS CODED)	DOSE	CAT. OF EVENT[a]	DAY[b]	DUR. OF EVENT (DAYS)	INTEN-SITY[c]	CAUSA-LITY[d]	COUNTERMEASURES		OUTCOME
											STUDY DRUG	OTHER	
[redacted]	[redacted]	[redacted]	[redacted]	Coronary occlusion	[redacted]	EXAC	12	18	Moderate	[redacted]	No change	Both	Subsided
5101	292	66	M	Db trt	Hyperglycemia	0	EXAC	18	25	Moderate	Possible	Perm. discont	Medicament	Subsided
				Db trt	Hyperglycemia	-	EXAC	18	25	Moderate	Possible	Perm. discont	Medicament	Subsided
5101	396	55	F	Db trt	Depression	6	EXAC	90	-	Moderate	None	No change	Medicament	Still present
5201	115	52	M	Db trt	Emotional lability	-	EXAC	2	-	Moderate	None	Perm. discont	None	Still present
				Db trt	Emotional lability	-	EXAC	2	-	Moderate	None	Perm. discont	None	Still present
5401	80	47	F	Db trt	Headache	1	NII	6	-	Mild	Possible	No change	None	Still present
5601	179	64	F	Db trt	Diarrhea	4	ADR	66	75	Severe	Possible	No change	Medicament	Subsided
				Db trt	Pruritus	4	ADR	66	75	Moderate	Possible	No change	None	Subsided
6401	93	55	F	Db trt	Gastritis	2	OTH	31	15	Moderate	Possible	No change	Medicament	Subsided
				Db trt	Pharyngitis	2	NII	31	10	Moderate	None	No change	Medicament	Subsided
6701	422	52	F	Db trt	Abnormal vision	6	ADR	85	0	Mild	Possible	No change	None	Subsided
				Db trt	Hypoglycemia	6	ADR	85	0	Mild	Possible	No change	None	Subsided
7201	117	54	M	Db trt	Back pain	6	NII	2	-	Moderate	None	No change	Medicament	Still present
				Db trt	Polyuria	-	ADR	108	-	Severe	Possible	Perm. discont	None	Still present

Note : Shading denotes a serious adverse event

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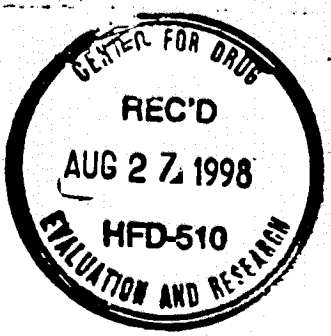


Dr Sobel

Hoechst Marion Roussel

August 25, 1998

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

Hoechst Marion Roussel, Inc.

10236 Marion Park Drive
Mail: P.O. Box 962
Kansas City, MO 64134-062
Telephone (816) 966-5000
U.S. Web site: www.hmri.com

Subject: **Amaryl® (glimepiride Tablets)**
NDA 20-496/Supplement 002
Additional information on the use of Amaryl concomitantly with metformin

Dear Dr. Sobel:

In reference to your letter to Dr. Michael Nicholas dated August 10, 1998, please find the enclosed abstract titled "Addition of Glimepiride Significantly Improves Glycaemic Control in Type 2 Diabetic Patients Insufficiently Controlled on Metformin" (*Diabetes*, volume 47, supp. 1, page A351, abstract 1355). You requested additional information from a small study of 3 months duration in at least 50 patients to support the use of Amaryl concomitantly with metformin when diet, exercise, and Amaryl or metformin alone do not result in adequate glycemic control.

This abstract describes a double-blind, randomized study conducted by Hoechst Marion Roussel associates in France. The study was 20 weeks in duration and compared the efficacy and safety of Amaryl given in combination with metformin to either drug given as monotherapy in 369 Type 2 diabetic patients. The frequency of symptomatic hypoglycemia was higher in patients receiving the combination therapy (22%) when compared to either drug alone (Amaryl, 13%; metformin, 12%). The percentage of patients with adverse events was 52.0% in the metformin group, 46.3% in the Amaryl group, and 48.3% in the combination group. The incidence of gastrointestinal adverse events was slightly higher in the metformin group (12.0%) when compared to the combination group (6.9%) and the Amaryl group (5.4%).

Please refer to the letter from Dan Henry, RPh dated November 3, 1997, for the prescribing information. At this time, no changes are planned based on the above information.

We understand that these changes to Amaryl Tablet labeling may not be implemented until we have been notified in writing that the supplement application is approved.

Please contact me at (816) 966-5381 if you have further questions or need additional information.

Sincerely,
Carol J. Childers

Carol Childers, PharmD
Associate Regulatory Analyst
US Regulatory Affairs, Marketed Products

Enclosure: Abstract titled "Addition of Glimepiride Significantly Improves Glycaemic Control in Type 2 Diabetic Patients Insufficiently Controlled on Metformin" (*Diabetes*, volume 47, supp. 1, page A351, abstract 1355)

~~RESUBMISSION~~ ORIGINAL

(SUPPL NEW CORRES

Hoechst Marion Roussel

SNC-002

Hoechst Marion Roussel, Inc.

10236 Marion Park Drive
Mail: P.O. Box 9627
Kansas City, MO 64134-0627
Telephone (816) 966-5000

February 12, 1998

Solomon Sobel, M.D.
Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrine Drug Products, HFD-510
Attention: DOCUMENT CONTROL ROOM
5600 Fishers Lane
Rockville, MD 20857

Subject: Amaryl® (glimepiride) Tablets
NDA 20-496
Resubmission of Prior Approval Supplement dated November 3, 1997

Dear Dr. Sobel:

Enclosed is the resubmission of the November 3, 1997 Prior Approval Supplement for the above referenced NDA, which provided for changes to the following sections: Clinical Pharmacology, Indications and Usage, Precautions, and Dosage and Administration.

We also refer to the Division's letter, dated January 27, 1998, requesting the appropriate User Fee for this Prior Approval Supplement and hereby notify the Division that payment has been submitted. We understand that the review for fileability will begin upon notification by the bank that payment was received.

If you have any questions or need additional information, please contact me at 816-966-7796 (FAX 816-966-6794).

Sincerely,

Dan Henry, RPh
Manager, US Regulatory Affairs
Marketed Products

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

NDA SUPPLEMENT ORIGINAL

Hoechst Marion Roussel

November 3, 1997

NDA NO 20496 REF. NO. 002

NDA SUPPL FOR SE1

Hoechst Marion Roussel, Inc.

10236 Marion Park Drive
Mail: P.O. Box 9627
Kansas City, MO 64134-0627
Telephone (816) 966-5000

Solomon Sobel, M. D
Director
Division of Metabolism and Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

This is entirely satisfactory. The supplement ought to be approved so far as this MO is concerned

CENTER FOR DRUG REC'D NOV 0 4 1997 HFD-510 EVALUATION AND RESEARCH

Subject: **Amaryl® (glimepiride Tablets)**
NDA 20-496
PRIOR APPROVAL SUPPLEMENT

Dear Dr. Sobel:

Enclosed please find the attached draft prescribing information for Amaryl Tablets. The intent of this correspondence is to file a Prior Approval Supplement requesting changes to the below noted sections of the Amaryl Tablet prescribing information.

In that Amaryl clinical exposure is limited, we are submitting annotated labeling references and literature references based on approved changes to the metformin prescribing information..

/S/ 3/5/98

The enclosed prescribing information has been revised to reflect the following proposed changes:

(Additions are highlighted for your convenience -see attachment)

CLINICAL PHARMACOLOGY

There are no changes in CMC pertaining issues noted as acceptable /S/ 16-MAR-1998

INDICATIONS AND USAGE

VN LOG 1-27-98 /S/

noted /S/ 2/11/98

PRECAUTIONS

DOSAGE AND ADMINISTRATION

AMARYL® - Metformin combination Therapy

We understand that these changes to Amaryl Tablet labeling may not be implemented until we have been notified in writing that this supplement application is approved.

If you have any questions or need additional information, please contact me at 816-966-7796 (FAX 816-966-6794)

Sincerely,

Dan Henry, RPH
Manager, US Regulatory Affairs, Marketed Products

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Enclosures:

Revised draft Amaryl Tablet prescribing information
Annotated draft Amaryl Tablet prescribing information and supporting data

Revised Draft
Annotated Draft
Reference List
TAB 1
TAB 2

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Johnston

Food and Drug Administration
Rockville MD 20857

NDA 20-496/S-002

Hoechst Marion Roussel Inc.
Attention: J. Michael Nicholas, Ph.D.
Director, U.S. Regulatory Affairs
10236 Marion Park Drive
Kansas City, MO 64134-0627

FEB 26 1998

Dear Dr. Nicholas:

We acknowledge receipt of your supplemental application for the following:

Name of Drug Product:	AMARYL (glimepiride tablets)
NDA Number:	NDA 20-496
Supplement Number:	S-002
Therapeutic Classification:	Standard
Date of Supplement:	November 3, 1997

You were notified via telephone on November 6, 1997, and in our letter dated January 27, 1998, that your supplemental application for Amaryl (glimepiride) was not accepted for filing due to non-payment of fees.

This is to inform you that the Agency has received all fees owed and your supplemental application has been accepted as of February 10, 1998.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 11, 1998, in accordance with 21 CFR 314.101(a). If the application is filed, the goal date under FDAMA will be February 10, 1999.

Please cite the NDA and supplement number listed above at the top of the first page for any communications concerning this application and address any correspondence to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: DOCUMENT CONTROL ROOM
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please contact Michael F. Johnston, R.Ph., Regulatory Management Officer, at (301) 827-6423.

Sincerely yours,

/S/ - 2/20/98

Enid Galliers
Supervisory Project Manager
Division of Metabolic and Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Johnston

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-496/S-002

JAN 27 1998

Hoechst Marion Roussel Inc.
Attention: J. Michael Nicholas, Ph.D.
Director, U.S. Regulatory Affairs
10236 Marion Park Drive
Kansas City, MO 64134-0627

Dear Dr. Nicholas:

We acknowledge receipt of your supplemental application for the following:

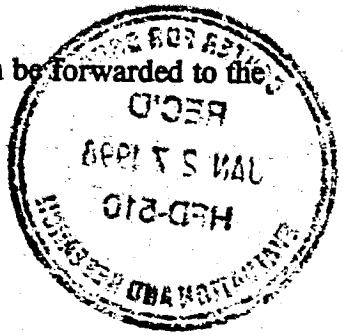
Name of Drug Product:	AMARYL (glimepiride tablets)
NDA Number:	NDA 20-496
Supplement Number:	S-002
Therapeutic Classification:	Standard
Date of Supplement:	November 3, 1997
Date of Receipt:	November 4, 1997

We have not received the appropriate user fee for this application. Under section 736(e) of the Prescription Drug User Fee Act of 1992 (PDUFA), as amended by the Food and Drug Administration Modernization Act of 1997, an application is considered incomplete and will not be accepted for filing until all fees owed have been paid. Therefore, this supplemental application is not accepted for filing. We will not begin a review of this supplemental application's adequacy for filing until FDA has been notified that the appropriate fee has been paid. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 360909
Pittsburgh, PA 15251-6909

If checks are to be sent by a courier that requires a street address, they can be forwarded to the following address:

Mellon Bank
Three Mellon Bank Center
27th Floor (FDA 360909)
Pittsburgh, PA 15259-0001



NOTE: **This address is for courier delivery only. Make sure the FDA Post Office Box Number (P.O. Box 360909) is on the enclosed check.**

The receipt date for this submission (which begins the review for fileability) will be the date the review division is notified that payment was received by the bank.

All communications concerning this supplemental application should be addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: DOCUMENT CONTROL ROOM
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please contact Michael F. Johnston, R.Ph., Regulatory Management Officer, at (301) 827-6423.

Sincerely yours,

/S/ 1/27/98

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research