3.2.P.8.1 Stability summary and conclusions

A Specifications at the end of shelf-life

TESTS	SPECIFICATIONS	
	AT THE RELEASE	AT THE END OF SHELF LIFE[5]
SHAPE	Oblong biconvex tablets, scored in one side and the inscription "1" in the other side.	Oblong biconvex tablets, scored in one side and the inscription "1" in the other side.
COLOUR	White	White
AVERAGE MASS	308,0 mg (293 -323 mg)	308,0 mg (293 -323 mg)
LOSS ON DRYING	NMT 5%	NMT 5%
IDENTIFICATION		
Risperidone[1]		
1 · HPLC(t_R)	Positive	Positive
2 · HPLC(UV)	Positive	Positive
3 · TLC	Positive	Positive
Titanium dioxide	Positive	Positive
DISSOLUTION	NLT 80% (Q) 30 min	NLT 80% (Q) 30 min
ASSAY (%)	95.0 – 105.0%	95.0 – 105.0%
(mg/tab)	0.950 -1.050 mg/tab	0.950 -1.050 mg/tab
UNIFORMITY OF DOSAGE UNITS	Ph. Eur. 2.9.40. AV NMT 15.0	Ph. Eur. 2.9.40. AV NMT 15.0
RELATED SUBSTANCES:		
· Impurity RIS 09	NMT 0.1%	NMT 0.1%
· Impurity RIS 10	NMT 0.1%	NMT 0.2%
· Any unspecified degradation product ……	NMT 0.1%	NMT 0.2%
· Total degradation products	NMT 0.5%	NMT 1.0%
MICROBIAL CONTAMINATION[2]		
· TAMC [3]	NMT 1000 CFU/g	NMT 1000 CFU/g
· TYMC [4]	NMT 100 CFU/g	NMT 100 CFU/g
· *Escherichia coli*	Absence/g	Absence/g

NMT: not more than NLT: not less than

(1) Identifications 1+2 or, alternatively 3.
(2) This test is performed on a minimum of one batch and a maximum of 3 batches a year of risperidone 1 mg tablets.
(3) Total Aerobic Microbial Count (Ph. Eur. 5.1.4)
(4) Total Yeasts and Moulds Count (Ph. Eur. 5.1.4)
(5) According to ICH guide ICH Q1A(R2), attributes that are not susceptible to change during storage, will not be included in on-going stability program.

TABLE 1(3.2.P.8.1).- Batch specifications at the release and at the end of shelf-life.

Note : the microbial contamination tests of the stability studies enclosed in section 3.2.P.8.3 are performed according to the old test since the new one was not applicable when the studies were designed.

3.2.P.8.2 Post-approval stability protocol and stability commitment

The stability study of batches manufactured in accelerated and long-term conditions must be conducted on three batches manufactured on an industrial scale, according to the aforementioned guideline. Currently, there are two industrial scale batches in on-going stability studies (accelerate and long-term conditions) as shown in sections *3.2.P.8.1* and *3.2.P.8.3.*

Consequently, as indicated in section *2.2.8 Stability Commitment (point 1)* of the aforementioned guideline, the long-term stability studies will be completed with a third industrial batch.

Laboratorios Lesvi, S.L. will have the results of the aforementioned studies at your disposal if they are required.

3.2.P.8.3 Stability data

A Stress testing

A.1 Characteristics studied, analytical methods and validation

Characteristics studied	Methods	Validation
Shape	**See 3.2.P.5.2 A.1**	**Not applicable.**
Colour	**See 3.2.P.5.2 A.2**	**Not applicable.**
Dissolution	**See 3.2.P.5.2 A.5**	**See 3.2.P.5.3 A**
Assay	**See 3.2.P.5.2 A.7**	**See 3.2.P.5.3 B**
Related substances	**See 3.2.P.5.2 A.9**	**See 3.2.P.5.3 D**

A.2 Results

Size	TESTS	Results
Risperidone 1 mg bulk tablets	SHAPE	Oblong, biconvex tablets scored in one side and the inscription "1" on the other side
	COLOUR.....	White
	DISSOLUTION.....	100 %
	ASSAY(%)	100.7 %
	(mg/tab).....	1.007mg/tab
	RELATED SUBSTANCES	
	Impurity RIS 09 (%).....	<0.01
	Impurity RIS 10 (%).....	0.10
	Any unspecified degradation product.....	Correct (Only a peak with t_{RR} =0.20:0.08%)
	Total degradation products (%).....	< 0.19
Risperidone 1 mg tablets. Protected bulk	SHAPE	Oblong, biconvex tablets scored in one side and the inscription "1" on the other side
	COLOUR.....	White
	DISSOLUTION.....	---
	ASSAY	---
	RELATED SUBSTANCES	
	Impurity RIS 09 (%).....	<0.01
	Impurity RIS 10 (%).....	0.07
	Any unspecified degradation product.....	Correct
	Total degradation products (%).....	<0.08

---: test not performed

TABLE 1(3.2.P.8.3).- Results of the photostability study for batch GAL03035

A.3 Comments on results

Among all tested samples, it has been detected a slight increase in degradation impurity RIS 10 content and of an unspecified degradation product with with t_{RR} =0.2 (relative retention time) only in samples in bulk. The obtained values have not been more than 0.1% in any case.

No variations were observed either in the assay and the pharmacotechnical parameters [Table 1 (3.2.P.8.3)].

B Stability studies in accelerating and intermediate conditions

B.1 Characteristics studied, analytical methods and validation

Characteristics studied	Methods	Validation
Shape	**See 3.2.P.5.2 A.1**	**Not applicable.**
Colour	**See 3.2.P.5.2 A.2**	**Not applicable.**
Average mass	**See 3.2.P.5.2 A.3**	**Not applicable.**
Loss on drying	**See 3.2.P.5.2 A.4**	**Not applicable.**
Disintegration	**See 3.2.P.3.4 A.1.1**	**Not applicable.**
Resistance to crushing	**See 3.2.P.3.4 A.1.1**	**Not applicable.**
Dissolution	**See 3.2.P.5.2 A.5**	**See 3.2.P.5.3 A**
Assay	**See 3.2.P.5.2 A.7**	**See 3.2.P.5.3 B**
Related substances	**See 3.2.P.5.2 A.9**	**See 3.2.P.5.3 D**
Microbial contamination	**See 3.2.P.5.2 A.10**	**See 3.2.P.5.3 E**

NOTE: The following tables show the results obtained in the conditions 25 ± 2°C/60 ± 5% RH and 40 ± 2°C/75 ± 5% RH in the different packs studied.

B.1 Results

3.2.P.8.3 Stability data

Protocol Number 237-03	**Product/Dose** Risperidone 1 mg tablets	**Batch Number** GAL03035	**Manufacturing Date** July 2003	**Container/Size/Closure System(description)** Aluminium/ Aluminium blister
Storage Conditions 25±2ºC/60±5HR	**Starting Material Batch** Risperidone G0322/PP-7M/P	**Batch Size** 136.000 tablets	**Stability Starting Date** 03-10-03	**Sample Orientation** Not applicable

TEST	Specifications	0	3	6	9	12	18	24	36	48
SHAPE ……	[1]	[1]	[1]	[1]	[1]	[1]	[1]	[1]	[1]	[1]
COLOUR……	White	White	White	White	White	White	White	White	White	White
AVERAGE MASS[2]……	308.0 mg (±5%)	307.9(±0.8%)	307.3(±1.0%)	307.3(±0.9%)	307.2(±1.3%)	307.5(±0.9%)	307.8(±0.8%)	307.7(±0.7%)	308.7(±1.1%)	308.4(±1.1%)
LOSS ON DRYING……..	≤ 5%	2.3	2.4	2.7	2.6	3.0	3.1	2.8	2.6	2.4
DISINTEGRATION[3] (min)……	< 30	2.4(2 – 3)	2.7(2 – 3)	2.6(2 – 4)	2.2(1 – 3)	2.2(1 – 3)	2.6(2 – 3)	2.4(1 – 3)	2.2(1 – 3)	1.9(1 – 2)
RESISTANCE TO CRUSHING[3] (N)…..	[4]	132 (113 – 147)	141 (127 – 152)	138 (129 – 149)	125 (97 – 146)	----	134 (125 – 140)	132 (121 – 143)	107 (97 – 117)	139 (129 – 150)
DISSOLUTION(%)……	(80%) 30 min	103	102	97	97	101	99	102	102	101
ASSAY(%)……	95.0 – 105.0	97.9	102.1	102.3	100.5	101.2	99.4	100.8	98.3	100.5
(mg/tab)	0.950-1.050	0.979	1.021	1.023	1.005	1.012	0.994	1.008	0.983	1.0055
RELATED SUBSTANCES										
Impurity RIS 09 (%)……	≤ 0.1	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	0.01	0.01
Impurity RIS 10 (%)……	≤ 0.2	<0.03	<0.05	<0.05	<0.05	0.06	0.07	0.09	0.09	0.10
Any unspecified degradation product…..	≤ 0.2	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1
Total degradation products (%)……	≤ 1.0	<0.04	<0.06	<0.06	<0.06	<0.07	<0.08	<0.10	0.19	0.11
MICROBIAL CONTAMINATION										
Total aerobic count (CFU/g)……....	≤1000	<10	-----	-----	-----	<10	-----	<10	<10	<10
Total fungi and yeast (CFU/g)……	≤ 100	< 10	-----	-----	-----	< 10	-----	< 10	< 10	< 10
Escherichia coli……	Absence/g	Absence/g	-----	-----	-----	Absence/g	-----	Absence/g	Absence/g	Absence/g

1: Oblong, biconvex tablets, scored in one side and the inscription "1" on the other side.
2: Mean and coefficient of variation.
3: Mean and range.
4: Information test, not defined specifications
--: test not performed

TABLE 2 (3.2.P.8.3).- Stability data for batch GAL03035 to 25ºC±2ºC/60%HR±5 %, on Aluminium/Aluminium blister.

3.2.P.8.3 Stability data

Protocol Number 238-03	**Product/Dose** Risperidone 1 mg tablets	**Batch Number** GAL03035	**Manufacturing Date** July 2003	**Container/Size/Closure System(description)** PVC/ Aluminium blister
Storage Conditions 25±2ºC/60±5HR	**Starting Material Batch** Risperidone G0322/PP-7M/P	**Batch Size** 136.000 tablets	**Stability Starting Date** 08-10-03	**Sample Orientation** Not applicable

TEST	Specifications	0	3	6	9	12	18	24	36	48
SHAPE ……	[1]	[1]	[1]	[1]	[1]	[1]	[1]	[1]	[1]	[1]
COLOUR……	White	White	White	White	White	White	White	White	White	White
AVERAGE MASS[2]……	308.0 mg (±5%)	307.9(±0.8%)	313.6(±0.8%)	312.3(±1.0%)	313.7(±0.8%)	311.9(±0.9%)	311.0(±1.0%)	312.1(±1.0%)	311.6(±1.1%)	312.5(±0.9%)
LOSS ON DRYING……..	≤ 5%	2.3	3.4	3.6	3.9	3.8	3.8	3.7	3.8	3.4
DISINTEGRATION[3] (min)……	< 30	2.4(2 – 3)	1.8(1 – 3)	1.7(1 – 2)	1.7(1 – 2)	1.8(1 – 2)	1.9(1 – 2)	1.8(1 – 2)	1.8(1 – 2)	1.8(1 – 2)
RESISTANCE TO CRUSHING[3] (N)….....	[4]	132 (113 – 147)	127 (114 – 139)	128 (116 – 141)	110 (97 – 122)	114 (107 – 124)	107 (94 – 117)	131 (124 – 144)	122 (110 – 136)	131 (115 – 144)
DISSOLUTION(%)……	(80%) 30 min	103	99	99	99	101	98	103	100	99
ASSAY(%)……	95.0 – 105.0	97.9	100.6	101.2	100.8	99.9	99.9	99.5	96.9	98.5
(mg/tab) .....….....	0.950-1.050	0.979	1.008	1.012	1.008	0.999	0.999	0.995	0.969	0.9845
RELATED SUBSTANCES										
Impurity RIS 09 (%)……..….	≤ 0.1	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	0.01
Impurity RIS 10 (%)……	≤ 0.2	<0.03	0.05	<0.05	0.06	0.06	0.11	<0.05	0.10	0.21
Any unspecified degradation product…..	≤ 0.2	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1
Total degradation products (%)……	≤ 1.0	<0.04	<0.06	<0.06	<0.07	<0.07	<0.12	<0.06	0.17	0.22
MICROBIAL CONTAMINATION										
Total aerobic count (CFU/g)…….....	≤1000	<10	-----	-----	-----	<10	-----	<10	<10	<10
Total fungi and yeast (CFU/g)……	≤ 100	< 10	-----	-----	-----	< 10	-----	< 10	< 10	< 10
Escherichia coli……..……	Absence/g	Absence/g	-----	-----	-----	Absence/g	-----	Absence/g	Absence/g	Absence/g

1: Oblong, biconvex tablets, scored in one side and the inscription "1" on the other side..
2: Mean and coefficient of variation.
3: Mean and range.
4: Information test, not defined specifications
--: test not performed

TABLE 3 (3.2.P.8.3).- Stability data for batch GAL 03035 to 25ºC±2ºC/60%HR±5 %, on PVC/Aluminium blister.

3.2.P.8.3 Stability data

Protocol Number 239-03	**Product/Dose** Risperidone 1 mg tablets	**Batch Number** GAL03035	**Manufacturing Date** July 2003	**Container/Size/Closure System(description)** Polyamide bags
Storage Conditions 25±2ºC/60±5HR	**Starting Material Batch** Risperidone G0322/PP-7M/P	**Batch Size** 136.000 tablets	**Stability Starting Date** 10-10-03	**Sample Orientation** Not applicable

TEST	Specifications	0	3	6
SHAPE ……	[1]	[1]	[1]	[1]
COLOUR……	White	White	White	White
AVERAGE MASS[2]……	308.0 mg (±5%)	307.9(±0.8%)	307.3(±1.4%)	307.1(±0.9%)
LOSS ON DRYING……..	≤ 5%	2.3	2.6	2.5
DISINTEGRATION[3] (min)……	< 30	2.4(2 – 3)	2.5(1 – 3)	2.4(2 – 3)
RESISTANCE TO CRUSHING[3] (N)……..	[4]	132 (113 – 147)	145 (126 – 160)	138 (128 – 156)
DISSOLUTION(%)……	(80%) 30 min	103	100	100
ASSAY(%)……....	95.0 – 105.0	97.9	102.4	102.3
(mg/tab)	0.950-1.050	0.979	1.024	1.023
RELATED SUBSTANCES				
Impurity RIS 09 (%)……..….	≤ 0.1	<0.01	<0.01	<0.01
Impurity RIS 10 (%)……	≤ 0.2	<0.03	≤0.03	0.05
Any unspecified degradation product…..	≤ 0.2	≤ 0.1	≤ 0.1	≤ 0.1
Total degradation products (%)……	≤ 1.0	<0.04	≤0.04	<0.06
MICROBIAL CONTAMINATION				
Total aerobic count (CFU/g)……...	≤1000	5	-----	< 10
Total fungi and yeast (CFU/g)……	≤ 100	< 10	-----	< 10
Escherichia coli……	Absence/g	Absence/g	-----	Absence/g

1: Oblong, biconvex tablets, scored in one side and the inscription "1" on the other side.
2: Mean and coefficient of variation.
3: Mean and range.
4: Information test, not defined specifications
--: test not performed

TABLE 4 (3.2.P.8.3).- Stability data for batch GAL 03035 to 25ºC±2ºC/60%HR±5 %, on Polyamide bags.

3.2.P.8.3 Stability data

Protocol Number 237-03	**Product/Dose** Risperidone 1 mg tablets	**Batch Number** GAL03035	**Manufacturing Date** July 2003	**Container/Size/Closure System(description)** Aluminium/ Aluminium blister
Storage Conditions 40±2ºC/75±5HR	**Starting Material Batch** Risperidone G0322/PP-7M/P	**Batch Size** 136.000 tablets	**Stability Starting Date** 03-10-03	**Sample Orientation** Not applicable

TEST	Specifications	0	3	6
SHAPE ……	[1]	[1]	[1]	[1]
COLOUR……	White	White	White	White
AVERAGE MASS[2]……	308.0 mg (±5%)	307.9(±0.8%)	308.1(±0.7%)	307.7(±0.7%)
LOSS ON DRYING……..	≤ 5%	2.3	2.4	2.6
DISINTEGRATION[3] (min)……	< 30	2.4(2 – 3)	2.4(2 – 3)	2.2(1 – 3)
RESISTANCE TO CRUSHING[3] (N)….....	[4]	132 (113 – 147)	142 (130 – 151)	137 (124 – 152)
DISSOLUTION(%)……	(80%) 30 min	103	102	100
ASSAY(%)……	95.0 – 105.0	97.9	100.2	100.5
(mg/tab)	0.950-1.050	0.979	1.002	1.005
RELATED SUBSTANCES				
Impurity RIS 09 (%)……..….	≤ 0.1	<0.01	<0.01	<0.01
Impurity RIS 10 (%)……	≤ 0.2	<0.03	0.10	0.14
Any unspecified degradation product…..	≤ 0.2	≤ 0.1	≤ 0.1	≤ 0.1
Total degradation products (%)……	≤ 1.0	<0.04	<0.11	<0.20
MICROBIAL CONTAMINATION				
Total aerobic count (CFU/g)…….....	≤1000	<10	-----	< 10
Total fungi and yeast (CFU/g)……..…	≤ 100	< 10	-----	< 10
Escherichia coli……	Absence/g	Absence/g	-----	Absence/g

1: Oblong, biconvex tablets, scored in one side and the inscription "1" on the other side..
2: Mean and coefficient of variation.
3: Mean and range.
4: Information test, not defined specifications
--: test not performed

TABLE 5 (3.2.P.8.3).- Stability data for batch GAL 03035 to 40ºC±2ºC/75%HR±5 %, on Aluminium/Aluminium blister.

3.2.P.8.3 Stability data

Protocol Number 238-03	**Product/Dose** Risperidone 1 mg tablets	**Batch Number** GAL03035	**Manufacturing Date** July 2003	**Container/Size/Closure System(description)** PVC/ Aluminium blister
Storage Conditions 40±2ºC/75±5HR	**Starting Material Batch** Risperidone G0322/PP-7M/P	**Batch Size** 136.000 tablets	**Stability Starting Date** 08-10-03	**Sample Orientation** Not applicable

TEST	Specifications	0	3	6
SHAPE ……	[1]	[1]	[1]	[1]
COLOUR……	White	White	White	White
AVERAGE MASS[2]……	308.0 mg (±5%)	307.9(±0.8%)	315.3(±0.8%)	315.5(±1.5%)
LOSS ON DRYING……..	≤ 5%	2.3	4.0	3.9
DISINTEGRATION[3] (min)……	< 30	2.4(2 – 3)	4.5(4 – 5)	8.2(6 – 11)
RESISTANCE TO CRUSHING[3] (N)….....	[4]	132 (113 – 147)	133 (115 – 153)	145 (132 – 163)
DISSOLUTION(%)……	(80%) 30 min	103	96	94
ASSAY(%)……	95.0 – 105.0	97.9	99.0	100.3
(mg/tab)	0.950-1.050	0.979	0.990	1.003
RELATED SUBSTANCES				
Impurity RIS 09 (%)…….….	≤ 0.1	<0.01	<0.01	<0.01
Impurity RIS 10 (%)……	≤ 0.2	<0.03	0.14	0.16
Any unspecified degradation product…..	≤ 0.2	≤ 0.1	≤ 0.1	≤ 0.1
Total degradation products (%)……	≤ 1.0	<0.04	<0.23	<0.24
MICROBIAL CONTAMINATION				
Total aerobic count (CFU/g)…….....	≤1000	<10	-----	< 10
Total fungi and yeast (CFU/g)……	≤ 100	< 10	-----	< 10
Escherichia coli……..……	Absence/g	Absence/g	-----	Absence/g

1: Oblong, biconvex tablets, scored in one side and the inscription "1" on the other side.
2: Mean and coefficient of variation.
3: Mean and range.
4: Information test, not defined specifications
--: test not performed

TABLE 6 (3.2.P.8.3).- Stability data for batch GAL 03035 to 40ºC±2ºC/75%HR±5 %, on PVC/Aluminium blister.

3.2.P.8.3 Stability data

Protocol Number 237-03	**Product/Dose** Risperidone 1 mg tablets	**Batch Number** GAL03036	**Manufacturing Date** July 2003	**Container/Size/Closure System(description)** Aluminium/ Aluminium blister
Storage Conditions 25±2ºC/60±5HR	**Starting Material Batch** Risperidone G0327/PP-8M/P	**Batch Size** 136.000 tablets	**Stability Starting Date** 03-10-03	**Sample Orientation** Not applicable

TEST	Specifications	0	3	6	9	12	18	24	36	48
SHAPE ……	[1]	[1]	[1]	[1]	[1]	[1]	[1]	[1]	[1]	[1]
COLOUR……	White	White	White	White	White	White	White	White	White	White
AVERAGE MASS[2]……	308.0 mg (±5%)	306.6(±1.3%)	305.8(±1.8%)	308.1(±1.8%)	308.1(±1.4%)	307.7(±1.4%)	306.2(±1.7%)	305.5(±1.3%)	307.0(±1.6%)	307.7(±1.6%)
LOSS ON DRYING……..	≤ 5%	2.5	2.7	2.7	2.9	3.3	2.7	2.9	2.6	2.6
DISINTEGRATION[3] (min)……	< 30	2.4(1 – 3)	2.1(1 – 3)	2.4(1– 3)	2.3(1– 3)	2.2(1– 3)	2.3(1– 3)	2.3(2 – 3)	1.8(1-3)	1.9(1 – 2)
RESISTANCE TO CRUSHING[3] (N)….....	[4]	110 (91 – 122)	124 (98 – 138)	122 (99 – 149)	117 (102 – 135)	114 (95 – 135)	117 (80 – 144)	111(98 – 125)	91(70 – 104)	123 (87 – 155)
DISSOLUTION(%)……	(80%) 30 min	103	101	98	98	100	99	103	101	100
ASSAY(%)……	95.0 – 105.0	100.5	100.9	101.4	100.6	101.4	98.6	101.0	98.4	101.0
(mg/tab)	0.950-1.050	1.005	1.009	1.014	1.006	1.014	0.986	1.010	0.984	1.0098
RELATED SUBSTANCES										
Impurity RIS 09 (%)…….….	≤ 0.1	<0.,01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	0.01
Impurity RIS 10 (%)……	≤ 0.2	<0.03	0.05	<0.05	0.05	0.06	0.08	0.09	0.10	0.11
Any unspecified degradation product…..	≤ 0.2	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1
Total degradation products (%)……	≤ 1.0	<0.04	<0.06	<0.06	<0.06	<0.07	<0.09	<0.10	0.17	0.12
MICROBIAL CONTAMINATION										
Total aerobic count (CFU/g)……....	≤1000	5	-----	-----	-----	<10	-----	<10	<10	<10
Total fungi and yeast (CFU/g)……	≤ 100	< 10	-----	-----	-----	< 10	-----	< 10	< 10	< 10
Escherichia coli……	Absence/g	Absence/g	-----	-----	-----	Absence/g	-----	Absence/g	Absence/g	Absence/g

1: Oblong, biconvex tablets, scored in one side and the inscription "1" on the other side.
2: Mean and coefficient of variation.
3: Mean and range.
4: Information test, not defined specifications
--: test not performed

TABLE 7 (3.2.P.8.3).- Stability data for batch GAL03036 to 25ºC±2ºC/60%HR±5 %, on Aluminium/Aluminium blister.

3.2.P.8.3 Stability data

Protocol Number 238-03	**Product/Dose** Risperidone 1 mg tablets	**Batch Number** GAL03036	**Manufacturing Date** July 2003	**Container/Size/Closure System(description)** PVC/ Aluminium blister
Storage Conditions 25±2ºC/60±5HR	**Starting Material Batch** Risperidone G0327/PP-8M/P	**Batch Size** 136.000 tablets	**Stability Starting Date** 08-10-03	**Sample Orientation** Not applicable

TEST	Specifications	0	3	6	9	12	18	24	36	48
SHAPE ……	[1]	[1]	[1]	[1]	[1]	[1]	[1]	[1]	[1]	[1]
COLOUR……	White	White	White	White	White	White	White	White	White	White
AVERAGE MASS[2]……	308.0 mg (±5%)	306.6(±1.8%)	312.0(±1.3%)	309.6(±1.4%)	311.4(±1.3%)	309.9(±1.4%)	308.8(±1.0%)	310.9(±1.5%)	311.2(±1.8%)	311.1(±1.1%)
LOSS ON DRYING……..	≤ 5%	2.5	3.4	3.5	4.0	3.8	3.8	3.7	3.8	3.3
DISINTEGRATION[3] (min)……	< 30	2.4(1 – 3)	1.8(1 – 3)	1.8(1 – 3)	1.5(1– 2)	1.6(1– 2)	1.6(1– 2)	1.9(1 – 2)	1.8(1 – 3)	1.6(1 – 2)
RESISTANCE TO CRUSHING[3] (N)……..	[4]	110 (91 – 122)	111 (87 – 129)	112 (89 – 128)	105 (94– 117)	106 (84 – 124)	97 (88 – 107)	106 (81 –136)	105 (82 –126)	123 (111 – 131)
DISSOLUTION(%)……	(80%) 30 min	103	98	100	100	104	102	100	101	98
ASSAY(%)……	95.0 – 105.0	100.5	100.6	100.6	100.2	99.7	99.7	99.6	96.3	98.5
(mg/tab)	0950-1.050	1.005	1.006	1.006	1.002	0.997	0.997	0.996	0.963	0.9850
RELATED SUBSTANCES										
Impurity RIS 09 (%)……..….	≤ 0.1	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	<0.01	0.01	0.01
Impurity RIS 10 (%)……	≤ 0.2	<0.03	<0.05	<0.05	0.06	0.07	0.07	<0.05	0.11	0.16
Any unspecified degradation product…..	≤ 0.2	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1	≤ 0.1
Total degradation products (%)……	≤ 1.0	<0.04	<0.06	<0.06	<0.07	<0.08	<0.08	<0.06	0.22	0.17
MICROBIAL CONTAMINATION										
Total aerobic count (CFU/g)……....	≤1000	5	-----		-----	<10	-----	<10	<10	<10
Total fungi and yeast (CFU/g)……	≤ 100	5	-----		-----	<10	-----	<10	<10	< 10
Escherichia coli……..……	Absence/g	Absence/g	-----		-----	Absence/g	-----	Absence/g	Absence/g	Absence/g

1: Oblong, biconvex tablets, scored in one side and the inscription "1" on the other side..
2: Mean and coefficient of variation.
3: Mean and range.
4: Information test, not defined specifications
--: test not performed

TABLE 8 (3.2.P.8.3).- Stability data for batch GAL03036 to 25ºC±2ºC/60%HR±5 %, on PVC/Aluminium blister.

3.2.P.8.3 Stability data

Protocol Number 239-03	**Product/Dose** Risperidone 1 mg tablets	**Batch Number** GAL03036	**Manufacturing Date** July 2003	**Container/Size/Closure System(description)** Polyamide bags
Storage Conditions 25±2ºC/60±5HR	**Starting Material Batch** Risperidone G0327/PP-8M/P	**Batch Size** 136.000 tablets	**Stability Starting Date** 10-10-03	**Sample Orientation** Not applicable

TEST	Specifications	0	3	6
SHAPE ……..……	[1]	[1]	[1]	[1]
COLOUR……	White	White	White	White
AVERAGE MASS[2]……	308.0 mg (±5%)	306.6(±1.8%)	307.7(±1.1%)	306.9(±1.5%)
LOSS ON DRYING……..	≤ 5%	2.5	2.8	2.7
DISINTEGRATION[3] (min)……	< 30	2.4(1 – 3)	2.3(1 – 3)	2.2(2 – 3)
RESISTANCE TO CRUSHING[3] (N)……..	[4]	110 (91 – 122)	127 (117 – 140)	134 (100 – 144)
DISSOLUTION(%)……	(80%) 30 min	103	94	100
ASSAY(%)……..……	95.0 – 105.0	100.5	100.3	102.6
(mg/tab)	0.950-1.050	1.005	1.003	1.026
RELATED SUBSTANCES				
Impurity RIS 09 (%)……..….	≤ 0.1	<0.,01	<0.01	<0.01
Impurity RIS 10 (%)……	≤ 0.2	<0.03	≤0.03	0.05
Any unspecified degradation product…..	≤ 0.2	≤ 0.1	≤ 0.1	≤ 0.1
Total degradation products (%)……	≤ 1.0	<0.04	≤0.04	<0.06
MICROBIAL CONTAMINATION				
Total aerobic count (CFU/g)…….....	≤1000	<10	-----	< 10
Total fungi and yeast (CFU/g)……	≤ 100	< 10	-----	< 10
Escherichia coli……..….	Absence/g	Absence/g	-----	Absence/g

1: Oblong, biconvex tablets, scored in one side and the inscription "1" on the other side..
2: Mean and coefficient of variation.
3: Mean and range.
4: Information test, not defined specifications
--: test not performed

TABLE 9 (3.2.P.8.3).- Stability data for batch GAL03036 to 25ºC±2ºC/60%HR±5 %, on Polyamide bags

3.2.P.8.3 Stability data

Protocol Number 237-03	**Product/Dose** Risperidone 1 mg tablets	**Batch Number** GAL03036	**Manufacturing Date** July 2003	**Container/Size/Closure System(description)** Aluminium/ Aluminium blister
Storage Conditions 40±2ºC/75±5HR	**Starting Material Batch** Risperidone G0327/PP-8M/P	**Batch Size** 136.000 tablets	**Stability Starting Date** 03-10-03	**Sample Orientation** Not applicable

TEST	Specifications	0	3	6
SHAPE ……..……	[1]	[1]	[1]	[1]
COLOUR……	White	White	White	White
AVERAGE MASS[2]……	308.0 mg (±5%)	306.6(±1.8%)	307.7(±1.3%)	305.7(±1.7%)
LOSS ON DRYING……..	≤ 5%	2.5	2.7	2.6
DISINTEGRATION[3] (min)……	< 30	2.4(1 – 3)	2.2(1 – 3)	1.9(1 – 3)
RESISTANCE TO CRUSHING[3] (N)……..	[4]	110 (91 – 122)	134 (108 – 156)	119 (93 – 139)
DISSOLUTION(%)……	(80%) 30 min	103	100	100
ASSAY(%)…….……	95.0 – 105.0	100.5	99.4	99.6
(mg/tab)	0.950-1.050	1.005	0.994	0.996
RELATED SUBSTANCES				
Impurity RIS 09 (%)……..….	≤ 0.1	<0,01	<0.01	<0.01
Impurity RIS 10 (%)……	≤ 0.2	<0,03	0.12	0.15
Any unspecified degradation product…..	≤ 0.2	≤ 0.1	≤ 0.1	≤ 0.1
Total degradation products (%)……	≤ 1.0	<0,04	<0.13	<0.16
MICROBIAL CONTAMINATION				
Total aerobic count (CFU/g)…….....	≤1000	5	-----	< 10
Total fungi and yeast (CFU/g)……	≤ 100	< 10	-----	< 10
Escherichia coli……..….	Absence/g	Absence/g	-----	Absence/g

1: Oblong, biconvex tablets, scored in one side and the inscription "1" on the other side..
2: Mean and coefficient of variation.
3: Mean and range.
4: Information test, not defined specifications
--: test not performed

TABLE 10 (3.2.P.8.3).- Stability data for batch GAL03036 to 40ºC±2ºC/75%HR±5 %, on Aluminium/Aluminium blister.

Protocol Number 238-03	**Product/Dose** Risperidone 1 mg tablets	**Batch Number** GAL03036	**Manufacturing Date** July 2003	**Container/Size/Closure System(description)** PVC/ Aluminium blister
Storage Conditions 40±2ºC/75±5HR	**Starting Material Batch** Risperidone G0327/PP-8M/P	**Batch Size** 136.000 tablets	**Stability Starting Date** 08-10-03	**Sample Orientation** Not applicable

TEST	Specifications	0	3	6
SHAPE ……	[1]	[1]	[1]	[1]
COLOUR……	White	White	White	White
AVERAGE MASS[2]……	308.0 mg (±5%)	306.6(±1.8%)	314.8(±1.4%)	313.2(±1.7%)
LOSS ON DRYING……..	≤ 5%	2.5	4.0	3.9
DISINTEGRATION[3] (min)……	< 30	2.4(1 – 3)	4.7(3 – 6)	7.1(5 – 12)
RESISTANCE TO CRUSHING[3] (N)…..	[4]	110 (91 – 122)	127 (108 – 141)	137 (115 – 161)
DISSOLUTION(%)……	(80%) 30 min	103	95	95
ASSAY(%)……	95.0 – 105.0	100.5	98.3	97.5
(mg/tab)	0.950-1.050	1.005	0.983	0.975
RELATED SUBSTANCES				
Impurity RIS 09 (%)…….….	≤ 0.1	<0,01	<0.01	<0.01
Impurity RIS 10 (%)……	≤ 0.2	<0,03	0.12	0.17
Any unspecified degradation product…..	≤ 0.2	≤ 0.1	≤ 0.1	≤ 0.1
Total degradation products (%)……	≤ 1.0	<0,04	<0.13	<0.36
MICROBIAL CONTAMINATION				
Total aerobic count (CFU/g)……..	≤1000	5	-----	< 10
Total fungi and yeast (CFU/g)……	≤ 100	5	-----	< 10
Escherichia coli……..……	Absence/g	Absence/g	-----	Absence/g

1: Oblong, biconvex tablets, scored in one side and the inscription "1" on the other side.
2: Mean and coefficient of variation.
3: Mean and range.
4: Information test, not defined specifications
--: test not performed

TABLE 11 (3.2.P.8.3).- Stability data for batch GAL03036 to 40ºC±2ºC/75%HR±5 %, on PVC/Aluminium blister.

B.3 Comments on the results

To date, no significant change of the shape and colour of the tablets has been observed in any of the conditions tested.

There is a slight increase in the mean weight of the tablets packed in PVC/Al blisters. This increase in the mean weight of the tablets is related to an increase in their moisture content.
In no case was the specification for the two parameters exceeded.

We also observed slight increase in resistance to crushing and an increase in the disintegration of the tablets packed in PVC/Al blisters in the conditions 40 ± 2ºC / 75 ± 5 % RH.
In no case was the specification described for this parameter exceeded.

To date, no significant change has been observed in any of the conditions tested for the dissolution of the tablets.

The analytical results obtained at 25 ± 2°C/60 ± 5% RH and 40 ± 2°C/75 ± 5% RH for the assay of the substance, remain within the proposed shelf-life specifications.

As for the content in impurities, we observe a slight increase in RIS 10 and total impurities; but the established limits are not exceeded in any of the packs and in any of the conditions tested.

The determination of microbial contamination is only performed at the start and end of the study for each batch in accelerated conditions at 40 ± 2ºC/75 ± 5% RH and annualy at 25 ± 2°C/60 ± 5% RH. All the results obtained to date comply with the microbiological quality requirements described in the European Pharmacopoeia for oral administration products.

For each of the batches tested, microbial contamination will be determined at the end of the stability study at 25 ± 2°C / 60 ± 5% RH.

Finally, no visual differences have been observed from the observation of the different types of blister and pack, at the start of the stability study and at the different monitoring times, for any of the batches and in any of the conditions studied.

B Batches and conditions studied

The following batches were used in the stability study. The results of this study are included in section 3.2.P.8.3.

BATCH	DATE OF MANUFACTURE	PLACE OF MANUFACTURE	BATCH SIZE	TYPE OF PACK
GAL03035	July, 2003	Laboratorios VITA, S.A.*	136,000 tabs	Al/Al blister
				PVC/Al
				Polyamide bag
GAL03036	July, 2003	Laboratorios VITA, S.A.*	136,000 tabs	Al/Al blister
				PVC/Al
				Polyamide bag

* Laboratorios Vita, S.A. has changed its name to Laboratorios Lesvi,S.L.

TABLE 2 (3.2.P.8.1).- Characteristics of the batches manufactured.

General methodology of the study

The following tests are performed to study the stability of the product:

A) STRESS TESTING

-Photostability studies with batch GAL03035

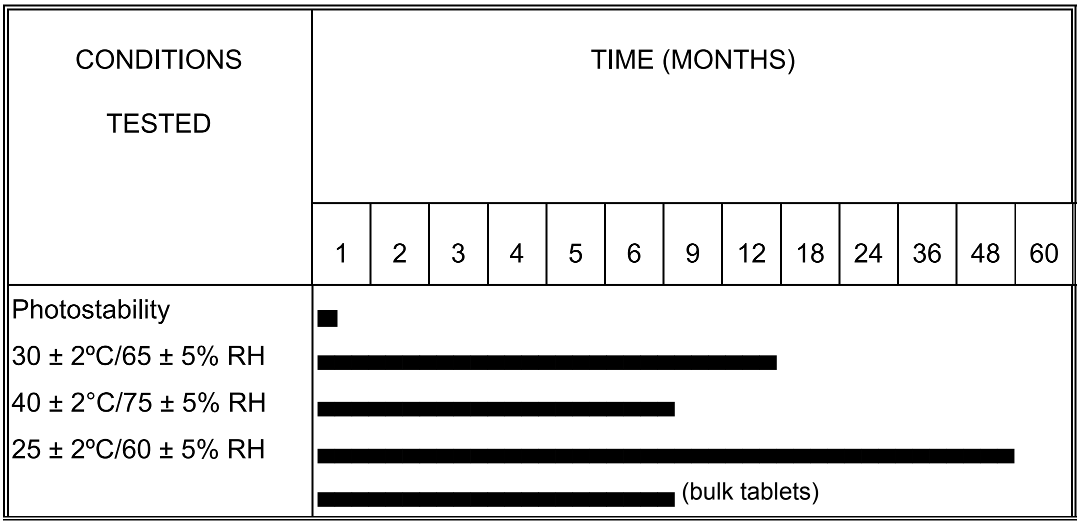
B) ACCELERATED TESTING

- Stability according to temperature and humidity (30 ± 2ºC / 65 ± 5 % RH, 12 months and 40 ± 2ºC / 75 ± 5 % RH, 6 months) with batches GAL03035 and GAL03036 packed in aluminium/aluminium blister and PVC/Aluminium blister.

C) LONG-TERM TESTING

- Stability at 25 ± 2°C and 60 ± 5% RH (48 months) in GAL03035 and GAL03036 packed in aluminium/aluminium blister and PVC/Aluminium blister.
- Stability at 25 ± 2°C and 60 ± 5% RH (6 months) in batches GAL03035 and GAL03036 of bulk tablets in a polyamide bag and inside a polypropylene drum together with a bag of a demoisturising agent.

Table 3 (3.2.P.8.1) summarises the conditions and duration times of the tests.



<u>TABLE 3(3.2.P.8.1)</u>.- Protocol of the conditions tested and duration of the tests.

A.1 **Stress testing**

A.1.1 ***Photostability***

DESCRIPTION OF THE EXPERIMENT

Samples from batch GAL03035 in bulk, in aluminium/aluminium blister, in PVC/Aluminium blister and samples for a negative light control (bulk samples protected from the light with aluminium foil but subject to the test's moisture conditions in the same way as the bulk samples, to distinguish between the changes produced by light and the changes produced by humidity) are placed in a photostability chamber and subjected for approximately 50 hours to the radiation (4 watt/m^2/time) from a near ultraviolet fluorescent lamp, and then exposed for 100 hours to the radiation (approx. 12 Klux /time) emitted by a white light fluorescent lamp.

Near ultraviolet energy received: not less than 200 Watt hours /m^2.
Total lighting: not less than 1.2 million lux hours.
Temperature / Humidity: 25ºC±2ºC/60% RH/±5% RH.

B.1 **Test in accelerated conditions**

B.1.1 ***Accelerated stability depending on temperature and moisture***

DESCRIPTION OF THE EXPERIMENT

Samples from batches GAL03035 and GAL03036 packed in aluminium/aluminium blister and PVC/Aluminium blister are stored in chambers at 40 ± 2ºC and 75 ± 5% RH and 30 ± 2ºC and 65 ± 5% RH. Samples are taken and analysed at regular intervals.

C.1 **Long term testing (real time)**

DESCRIPTION OF THE EXPERIMENT

Samples from batches GAL03035 and GAL03036 packed in aluminium/aluminium blister and PVC/Aluminium blister are stored in a chamber at 25 ± 2ºC and 60 ± 5% RH. Samples are taken and analysed at regular intervals.

Samples of the batches GAL03035 and GAL03036 in bulk in a polyamide bag and inside a polypropylene drum, together with a bag of demoisturing agent, are stored in a chamber at 25 ± 2ºC and 60 ± 5% RH. Samples are taken and analysed at regular intervals.

C Conclusions

a) During the photostability assay, it is observed that the bulk samples show a slight increase in impurity RIS 10, 0.10 % and of an unspecified degradation product, 0.08%; with regard to the bulk samples protected from the light.

b) In the stability studies in accelerated conditions, the tablets packed in PVC/Al blisters show a slight increase in the mean weight, loss on drying, disintegration and resistance to crushing values, related to the tablets absorption of water due to the permeability to water vapour of this packaging material.
The values obtained for these parameters are always within the described specifications.

The other pharmacotechnical parameters studied did not present significant variations from the initial values.

In the studies conducted with tablets packed in Al/Al blisters, we did not observe significant variations in any of the pharmacotechnical parameters from the initial values.

In the stability studies in accelerated conditions, in the conditions and containers studied, we observed a slight increase in the content in impurity RIS 10; however, these values remained beneath 0.2 %, the impurity RIS 09 remained without changes, lower than the detection limit.

As for the content in total impurities, although an increase is detected in both batches with Aluminium/Aluminium blister and PVC/Aluminium blister, in no case did the increase exceed the specified value of 1.0 %.

With regards to unspecified degradation products, in no case did the increase exceed the specified value of 0.2 %.

The results obtained in the assay of the active substance showed no significant changes in any of the batches studied, according to the ICH Q1A(R2) guide.

The microbiological characteristics remain within the limits of Eur. Ph. category 3A.

As the finished product was into specifications stored 6 months at accelerated conditions no information beyond 6 months has been generated at intermediate conditions.

c) In the long-term stability studies, the tablets packed in PVC/Al show a slight increase in the mean weight and loss on drying values, related to the tablets absorption of water due to the permeability to water vapour of this packaging material. The values obtained for these parameters are always within the described specifications.
The other pharmacotechnical parameters studied did not present significant variations from the initial values.

In the studies conducted with tablets packed in Al/Al blisters, we did not observe significant variations in any of the pharmacotechnical parameters from the initial values.

During the long-term stability studies, carried out to date, in no case is a substantial increase detected in the content of impurities, either individual or total, in relation to the initial values.

As for the assay parameter, in none of the batches studied were there significant changes, according to the ICH Q1A(R2) guide.

In the studies conducted with bulk tablets in polyamide bags, we did not observe significant variations in any of the pharmacotechnical parameters from the initial values. No differences were observed in relation to the initial values in the assay of the active substance and in the degradation impurities values.

The microbiological characteristics remain within the limits of Eur. Ph. category 3A.

D Proposed shelf-life

In view of the results obtained to date in the above stability studies, we propose a four year shelf life for the product.

E Storage conditions

The results obtained to date indicate that the product stored in its final containers does not require special storage conditions.