

**Executive CAC Meeting Minutes**

Date of Meeting: May 1, 2007

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair  
Joseph Contrera, Ph.D., OPS, Member  
Abby Jacobs, Ph.D., OND IO, Member  
Paul Brown, Ph.D., DDDP, Alternate Member  
Lois Freed, Ph.D., DNP, Supervisor  
David Hawver, Ph.D., DNP, Presenting Reviewer

Author of Draft: David Hawver, Ph.D.

The following information reflects a brief summary of the Committee's discussion and its recommendations.

NDA #: 22-083  
Drug Name: Exelon<sup>®</sup> Patch, Rivastigmine  
Sponsor: Novartis Pharma AG

**Background:**

Oral rivastigmine is a cholinesterase inhibitor currently marketed for the treatment of dementia of Alzheimer's disease and Parkinson's disease. A 99-week dermal carcinogenicity study in mouse was submitted to support an NDA for a new dermal formulation of rivastigmine, Exelon<sup>®</sup> Patch.

**Mouse Dermal Carcinogenicity Study:**

CD-1 mice (50/sex/group) were treated with rivastigmine via dermal application in 100% ethanol at doses of 0, 0.25, 0.50, and 0.75 mg/kg/day once daily for 99 weeks; an untreated control group was also included. The high dose of 0.75 mg/kg/day was expected to be close to the maximum tolerated dose (MTD), since a single dermal dose of 1.6 mg/kg/day rivastigmine was lethal in a previous 13-week mouse study. The carcinogenicity study appeared to be adequately performed. No treatment-related neoplastic or non-neoplastic findings were observed. The Statistical Reviewer concurred that no treatment-related neoplastic findings were observed.

**Executive CAC Recommendations and Conclusions:**

- The Committee noted that the study was terminated early (at Week 99) based on survival in control groups reaching 25/50. Although this is not considered sufficient cause for early termination, the Committee concluded that the study was adequate.
- The Committee agreed that doses were appropriate and that the study was negative for carcinogenicity since there were no treatment-related tumor findings.

David Jacobson-Kram, Ph.D.  
Chair, Executive CAC

### 2.6.6.6 Reproductive and developmental toxicology

No new studies were submitted.

### 2.6.6.7 Local tolerance

#### Acute dermal irritation in the rabbit

(Study Report 95/SPM080/1248; \_\_\_\_\_)

Dosing commenced 31 OCT 1995; GLP UK 1989, OECD 1981; QA; SDZ ENA 713  
TDS Batch #X 135 0595, Purity 100.5%)

b(4)

#### Key Points

- Application of one SDZ ENA 713 patch (18 mg/10 cm<sup>2</sup>) to the back of rabbits for 4 hrs induced only very slight erythema (in 3/3) and very slight edema (in 1/3).
- Placebo patches applied to the same rabbits for 4 hrs induced no skin reaction.

#### Methods

New Zealand White rabbits (N=3; ~3 months old; 2.36-2.95 kg) were treated with one 10 cm<sup>2</sup> placebo patch and one SDQ ENA 713 patch (18 mg/10 cm<sup>2</sup>), both applied to the closely clipped dorsum and protected by a semi-occlusive bandage. Patches were removed after 4 hrs and dermal reactions were assessed at 1, 24, 48, and 72 hrs after removal of the dressings.

#### Results

Very slight erythema was observed at 1 and 24 hr post-removal of the SDQ ENA 713 patch in all 3 rabbits, and edema was observed in one animal at 1 hr. All sites were normal at 48 hrs post-removal. No reactions were seen at the site of placebo patches in any animal at any time.

The study authors concluded that the test article was non-irritant, based on the very slight severity of the skin reactions observed.

This reviewer concurs.

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**Acute dermal irritation in rabbits**

(Study Report 0320061; ~~Project #506237~~; ~~\_\_\_\_\_~~  
 Dosing commenced 17 NOV 2003; GLP OECD, signed 2004; QA; SDZ ENA 713 TDS  
 Batch #8/22063/02, Purity 102.2%)

b(4)

Key Points

- Application of one SDZ ENA 713 patch (18 mg/10 cm<sup>2</sup>) to the back of rabbits for 4 hrs induced well-defined to moderate to severe erythema (in 3/3) and very slight to moderate edema (in 3/3).
- Placebo patches applied to the same rabbits for 4 hrs induced very slight to well-defined erythema (3/3) and slight edema (1/3).

Methods

New Zealand White rabbits (N=3M; ~3 months old; 2.25-2.38 kg) were treated with one 10 cm<sup>2</sup> placebo patch and one SDQ ENA 713 patch (18 mg/10 cm<sup>2</sup>), both applied to the closely clipped dorsum and protected by semi-occlusive tape and elastic bandage wrapped around the torso. Patches were removed after 4 hrs and dermal reactions were assessed at 1, 24, 48, and 72 hrs, and 5, 6, and 7 days after removal of the dressings.

Results

At SDQ ENA 713 patch sites, well-defined to moderate to severe erythema was noted in 3/3 at 1 hr, enduring at decreased severity through 24 hr, 72 hr, or Day 6. Very slight to moderate edema was noted on all 3 rabbits through 24, 48, or 72 hrs post-removal. At placebo patch sites, very slight to well-defined (Grade 2) erythema was noted in 3/3, and lasted through 1, 24, or 72 hrs; slight edema observed in 1/3 lessened to very slight at 48 hrs and disappeared by 72 hrs post-removal. The study authors concluded that the test article was “essentially non-irritating to the skin.”

Test Site

Animal	Body Weight at Dosing (kg)	Time after Patch Removal/Reaction Score													
		Erythema							Oedema						
		1 h	24 h	48 h	72 h	Day 5	Day 6	Day 7	1 h	24 h	48 h	72 h	Day 5	Day 6	Day 7
1	2.58	2	2	1	1	1	1	0	3	3	1	1	0	0	0
2	2.56	2	2	1	1	-	-	0	1	1	1	0	-	-	0
3	2.46	3	2	0	0	-	-	-	2	1	0	0	-	-	-

Control Site

Animal	Time after Patch Removal/Reaction Score													
	Erythema							Oedema						
	1 h	24 h	48 h	72 h	Day 5	Day 6	Day 7	1 h	24 h	48 h	72 h	Day 5	Day 6	Day 7
1	2	2	1	1	0	0	0	2	2	1	0	0	0	0
2	2	2	0	0	-	-	0	0	0	0	0	-	-	0
3	1	0	0	0	-	-	-	0	0	0	0	-	-	-

(Page 15 of Study Report)

**Primary skin irritation study in rabbits (4-hour semi-occlusive application)**

(Study Report 646740; \_\_\_\_\_)

Dosing commenced 20 JAN 1997; GLP FDA 1991; QA; SDZ ENA 713 TDS Batch #2409-1)

b(4)

Key Points

- Application of one SDZ ENA 713 patch (18 mg/10 cm<sup>2</sup>) to the back of rabbits for 4 hrs induced erythema (very slight to well-defined, in 3/3) and edema (very slight, in 2/3)
- Erythema lasted up to 14 days, edema up to 3 days.
- Based on the mean primary irritation score of 1.44, the SDZ ENA 713 patch was considered “non-irritating” to rabbit skin.

Methods

New Zealand White rabbits (N=1M, 2F; 15 wks old; 2.8-3.2 kg) were treated with one SDQ ENA 713 patch (18 mg/10 cm<sup>2</sup>), applied to the closely clipped dorsum and protected by an adhesive elastic semi-occlusive bandage. Patches were removed after 4 hrs and dermal reactions were assessed one hr, 24 hrs, 48 hrs, 72 hrs, 7 days, and 14 days after removal of the dressings. The primary irritation score was calculated by averaging the scores recorded at 24, 48, and 72 hrs post-removal.

Results

Removal of the patch was difficult, and caused red and blue discoloration on the skin of all 3 animals, along with erythema (3/3) lasting up to 14 days, and edema (2/3) lasting up to 3 days. One animal showed small wounds followed by scabbing. The skin at the test site was shiny and sticky for several days after patch removal. The mean primary irritation score was 1.44 (1.00 for erythema + 0.44 for edema). Based on this score, the test article was considered to be “not irritating” to rabbit skin. All skin reactions were attributed to mechanical injuries caused by the removal of the tightly adhering patch.

**Table 1.**

Animal Number	Sex	Mean Values: 24 - 72 Hours	
		Erythema	Edema
1	male	0.33	0.00
2	female	1.33	0.33
3	female	1.33	1.00

*(Page 16 of Study Report)*

**Primary skin irritation study in rabbits (4-hour semi-occlusive application)**

(Study Report 646751;

Dosing commenced 20 JAN 1997; GLP FDA 1991; QA; SDZ ENA 713 TDS Batch #2415-1)

**b(4)**

Key Points

- Application of one SDZ ENA 713 patch (18 mg/10 cm<sup>2</sup>) to the back of rabbits for 4 hrs induced erythema (very slight to well-defined, in 3/3) and edema (very slight, in 2/3)
- Erythema lasted up to 7 days, edema up to 3 days.
- Based on the mean primary irritation score of 1.88, the SDZ ENA 713 patch was considered “non-irritating” to rabbit skin.

Methods

New Zealand White rabbits (N=1M, 2F; 15 wks old; 3.0-3.3 kg) were treated with one SDQ ENA 713 patch (18 mg/10 cm<sup>2</sup>), applied to the closely clipped dorsum and protected by an adhesive elastic semi-occlusive bandage. Patches were removed after 4 hrs and dermal reactions were assessed one hr, 24 hrs, 48 hrs, 72 hrs, 7 days, and 14 days after removal of the dressings. The primary irritation score was calculated by averaging the scores recorded at 24, 48, and 72 hrs post-removal.

Results

Removal of the patch was difficult, and caused red and blue discoloration on the skin of all 3 animals, along with very slight to well-defined erythema (3/3) lasting up to 7 days, and very slight edema (2/3) lasting up to 3 days. The skin at the test site was shiny and sticky for 48 hrs after patch removal. The mean primary irritation score was 1.89 (1.44 for erythema + 0.44 for edema). Based on this score, the test article was considered to be “not irritating” to rabbit skin. All skin reactions were attributed to mechanical injuries caused by the removal of the tightly adhering patch.

**Table 1.**

Animal Number	Sex	Mean Values: 24 - 72 Hours	
		Erythema	Edema
4	male	1.00	0.00
5	female	2.00	1.00
6	female	1.33	0.33

*(Page 16 of Study Report)*

**Primary skin irritation study in rabbits (4-hour semi-occlusive application)**

(Study Report 646762; \_\_\_\_\_)

Dosing commenced 20 JAN 1997; GLP FDA 1991; QA; SDZ ENA 713 TDS Batch #2421-1)

**b(4)**Key Points

- Application of one SDZ ENA 713 patch (18 mg/10 cm<sup>2</sup>) to the back of rabbits for 4 hrs induced erythema (very slight to well-defined, in 3/3) and edema (very slight to slight, in 3/3)
- Erythema lasted up to 14 days, edema up to 14 days.
- Based on the mean primary irritation score of 2.33, the SDZ ENA 713 patch was considered "non-irritating" to rabbit skin.

Methods

New Zealand White rabbits (N=1M, 2F; 15 wks old; 2.8-3.1 kg) were treated with one SDQ ENA 713 patch (18 mg/10 cm<sup>2</sup>), applied to the closely clipped dorsum and protected by an adhesive elastic semi-occlusive bandage. Patches were removed after 4 hrs and dermal reactions were assessed one hr, 24 hrs, 48 hrs, 72 hrs, 7 days, and 14 days after removal of the dressings. The primary irritation score was calculated by averaging the scores recorded at 24, 48, and 72 hrs post-removal.

Results

Removal of the patch was difficult, and caused red and blue discoloration on the skin of all 3 animals, along with very slight to well-defined erythema (3/3) lasting up to 14 days, and very slight to slight edema (3/3) lasting up to 14 days. The skin at the test site was shiny and sticky in 2/3 animals for 24 hrs after patch removal. Slight to moderate scaling was noted in 2/3 rabbits. The mean primary irritation score was 2.33 (1.33 for erythema + 1.00 for edema). Based on this score, the test article was considered to be "not irritating" to rabbit skin. All skin reactions were attributed to mechanical injuries caused by the removal of the tightly adhering patch.

**Table 1.**

Animal Number	Sex	Mean Values: 24 - 72 Hours	
		Erythema	Edema
7	male	1.00	0.67
8	female	1.33	0.67
9	female	1.67	1.67

*(Page 16 of Study Report)*

**Primary skin irritation study in rabbits (4-hour semi-occlusive application)**

(Study Report 646773)

Dosing commenced 20 JAN 1997; GLP FDA 1991; QA; SDZ ENA 713 TDS Batch #2427-1)

b(4)

Key Points

- Application of one SDZ ENA 713 patch (18 mg/10 cm<sup>2</sup>) to the back of rabbits for 4 hrs induced erythema (very slight, in 3/3) and edema (very slight, in 1/3).
- Erythema lasted up to 7 days, edema up to 3 days.
- Based on the mean primary irritation score of 1.22, the SDZ ENA 713 patch was considered “non-irritating” to rabbit skin.

Methods

New Zealand White rabbits (N=1M, 2F; 15 wks old; 2.8-3.1 kg) were treated with one SDQ ENA 713 patch (18 mg/10 cm<sup>2</sup>), applied to the closely clipped dorsum and protected by an adhesive elastic semi-occlusive bandage. Patches were removed after 4 hrs and dermal reactions were assessed one hr, 24 hrs, 48 hrs, 72 hrs, 7 days, and 14 days after removal of the dressings. The primary irritation score was calculated by averaging the scores recorded at 24, 48, and 72 hrs post-removal.

Results

Removal of the patch was difficult, and caused red and blue discoloration on the skin of all 3 animals, along with very slight erythema (3/3) lasting up to 7 days, and very slight edema (1/3) lasting up to 3 days. The skin at the test site was shiny and/or sticky in all animals for 24-48 hrs after patch removal. Slight scaling was noted in 1/3 rabbits on Day 7. The mean primary irritation score was 1.22 (0.89 for erythema + 0.33 for edema). Based on this score, the test article was considered to be “not irritating” to rabbit skin. All skin reactions were attributed to mechanical injuries caused by the removal of the tightly adhering patch.

**Table 1.**

Animal Number	Sex	Mean Values: 24 - 72 Hours	
		Erythema	Edema
10	male	1.00	1.00
11	female	0.67	0.00
12	female	1.00	0.00

*(Page 16 of Study Report)*

**Primary skin irritation study in rabbits (4-hour semi-occlusive application)**

(Study Report 646784: \_\_\_\_\_)

Dosing commenced 20 JAN 1997; GLP FDA 1991; QA; SDZ ENA 713 TDS Batch #2437-1)

b(4)

Key Points

- Application of one SDZ ENA 713 patch (18 mg/10 cm<sup>2</sup>) to the back of rabbits for 4 hrs induced erythema (very slight to well-defined, in 3/3) and edema (very slight, in 3/3).
- Erythema lasted up to 14 days, edema up to 3 days.
- The mean primary irritation score was 2.33. The degree of erythema noted in 2/3 animals exceeded the criteria necessary to be considered "irritating" to rabbit skin, but the irritation was attributed to the mechanical injury involved in removal of the patch rather than to the drug substance.

Methods

New Zealand White rabbits (N=1M, 2F; 15 wks old; 3.1-3.2 kg) were treated with one SDQ ENA 713 patch (18 mg/10 cm<sup>2</sup>), applied to the closely clipped dorsum and protected by an adhesive elastic semi-occlusive bandage. Patches were removed after 4 hrs and dermal reactions were assessed one hr, 24 hrs, 48 hrs, 72 hrs, 7 days, and 14 days after removal of the dressings. The primary irritation score was calculated by averaging the scores recorded at 24, 48, and 72 hrs post-removal.

Results

Removal of the patch was difficult, and caused red and blue discoloration on the skin of all 3 animals, along with very slight to well-defined erythema (3/3) lasting up to 14 days, and very slight to slight edema (3/3) lasting up to 3 days. The skin at the test site was shiny and/or sticky in all animals for 2-14 days after patch removal. Slight to marked scaling was noted in one rabbit, and skin fissures in another. The mean primary irritation score was 2.67 (1.78 for erythema + 0.89 for edema). The degree of erythema noted in 2/3 animals exceeded the criteria necessary to be considered "irritating" to rabbit skin, but the irritation was attributed to the mechanical injury involved in removal of the patch rather than to the drug substance. All skin reactions were attributed to mechanical injuries caused by the removal of the tightly adhering patch.

**Table 1.**

Animal Number	Sex	Mean Values: 24 - 72 Hours	
		Erythema	Edema
13	male	2.00	1.00
14	female	1.33	0.33
15	female	2.00	1.33

*(Page 16 of Study Report)*

**Primary skin irritation study in rabbits (4-hour semi-occlusive application)**

(Study Report 640697)

Dosing commenced 18 NOV 1996; GLP FDA 1991; QA; SDZ ENA 713 TDS Batch #X 087 0496, Purity 102.3%)

b(4)

Key Points

- Application of one SDZ ENA 713 patch (18 mg/10 cm<sup>2</sup>) and one placebo patch to the back of rabbits for 4 hrs induced similar degrees of erythema in all animals (very slight to well-defined)
- Edema was very slight to well-defined in 3/3 SDZ ENA 713 patch animals and very slight in 2/3 placebo patch animals.
- Skin irritation was still present 7 days after patch removal, but 14 days.

Methods

New Zealand White rabbits (N=1M, 2F; 16 wks old; 3.1-3.2 kg) were treated with one 10 cm<sup>2</sup> placebo patch and one SDQ ENA 713 patch (18 mg/10 cm<sup>2</sup>), both applied to the closely clipped dorsum and protected by separate overlaminates and wrapped with a semi-occlusive elastic bandage around the abdomen, secured with tape. Patches were removed after 4 hrs and dermal reactions were assessed one hr, 24 hrs, 48 hrs, 72 hrs, 7 days, and 14 days after removal of the dressings. A primary irritation score was calculated by averaging the scores at 24, 48, and 72 hrs.

Results

The primary irritation score for the SDZ ENA 713 patch site was 3.22 (1.78 for erythema + 1.44 for edema), and the score for the placebo patch site was 2.67 (2.00 for erythema + 0.67 for edema). Erythema and edema were reversible after 14 days. The patches adhered strongly to the skin, and red and blue discoloration of the skin was noted upon removal. The test sites were both shiny at 7 days post-removal, but normal by 14 days. Both SDZ ENA 713 and placebo patches were considered to be irritating to the skin.

Animal No.	Mean values 24 - 72 hours			
	SDZ ENA 713 Left Flank Erythema	Edema	PLACEBO Right Flank Erythema	Edema
22, male	1.33	1.00	2.00	0.00
23, female	2.00	2.00	2.00	1.00
24, female	2.00	1.33	2.00	1.00

(Page 11 of Study Report)

**Primary skin irritation with SDZ ENA 713 TDS in rabbits (24 hour semi-occlusive application)**

(Study Report 282060, \_\_\_\_\_)

Dosing commenced 08 OCT 1990; GLP Switzerland 1986, EPA 1989; QA; SDZ ENA 713 TDS Batch #W0730890)

b(4)

Key Points

- Application of one SDZ ENA 713 TDS patch (4 cm<sup>2</sup>) to the back of three rabbits for 24 hrs did not induce any detectable skin reaction.

Methods

New Zealand White rabbits (N=2M, 1F; 15-16 wks old; 2.7-3.2 kg) were treated with one SDQ ENA 713 TDS patch (4 cm<sup>2</sup>), applied to the closely clipped dorsum and protected by a semi-occlusive dressing wrapped around the torso and secured with an elastic bandage. Patches were removed after 24 hrs and the site was flushed with 70% ethanol. Dermal reactions were assessed at 1, 24, 48, and 72 hrs post-removal.

Results

No signs of erythema or edema were observed at the test site of any of the 3 rabbits treated at any time point.

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**Contact hypersensitivity in albino guinea pigs modified buehler method.**

(Study report 640686; \_\_\_\_\_)

Dosing commenced 18 NOV 1996; GLP FDA 1991; QA; SDZ ENA 713 TDS Batch #X 087 0496, Purity 102.3%)

**Key Points**

- Application of the full-sized patch (18 mg/10 cm<sup>2</sup>) to guinea pigs (0.25-3 kg) resulted in death or moribund sacrifice of 3/20 within one or two days of the 24-hr treatment.
- Slight to moderate erythema was observed after both placebo and SDZ ENA 713 patch treatment during the induction phase.
- No skin reactions were seen during the challenge phase, suggesting that no sensitization occurred.
- The validity of this study is questionable due to uncertainties in the protocol modification to change the size of the patch after the first induction treatment.

**Methods**

Ibm: GOHI guinea pigs (N=10F Placebo, and 20 F Drug); 5-7 wks old; 244-294 g) were treated with one Placebo patch (10 cm<sup>2</sup>) or one SDZ ENA 713 TDS patch (18 mg/10 cm<sup>2</sup>), applied to the shaved dorsum (pretreated with 10% sodium-lauryl-sulfate in paraffinum perliquidum during the sensitization induction phase) and covered by an elastic plaster which was wrapped around the trunk of the animal and secured with an impervious adhesive tape. Patches were removed after 24 hrs. During the 3-wk induction phase, one treatment was given per week. Due to deaths after the first induction application of the 10 cm<sup>2</sup> patch, the second and third induction treatments were performed with one-quarter sized patches (4.5 mg/2.5 cm<sup>2</sup>). Two weeks after the 3<sup>rd</sup> induction application, the test and control animals were challenged with both a test article and a placebo patch (one on each flank). Dermal reactions were assessed at 24 and 48 hrs after removal of the challenge patches.

**Results**

2/20 SDZ ENA 713 TDS patch animals were found dead on test day 2, and 1/18 was killed in extremis on test day 3 (signs included emaciation, sedation, ruffled fur, and lid half closed). Another animal was found dead on test day 10, after the second application on Day 8. The deaths were considered test-article related.

After the first induction treatment, erythema was observed at the application site in all Placebo animals (6/10 slight, 4/10 moderate) and in all SDZ ENA 713 animals (8/17 slight, 9/17 moderate).

After the second induction treatment, erythema was observed at the application site in some Placebo animals (4/10 slight, 0/10 moderate) and in some SDZ ENA 713 animals (6/16 slight, 2/16 moderate).

After the third induction treatment, erythema was observed at the application site in some Placebo animals (3/10 slight, 0/10 moderate) and in some SDZ ENA 713 animals (4/16 slight, 0/16 moderate). No edema was observed at any time point in any group.

The erythema observed during the induction phase was attributed to the sodium-lauryl-sulfate pretreatment, which caused mild inflammation, and to the strong adhesion of the patches during removal from the skin.

After the challenge treatments, no erythema or edema was observed at the application site in any animal of any group.

*Reviewer's Note:* The dramatic change in dosing (from one patch per animal to one quarter patch per animal) was not well documented. It is not clear whether the challenge dosing was performed with whole patches or quarter patches, or if the second and third placebo induction treatments were performed with quarter-sized placebo patches. The descriptions in the "Results" section and the data tables failed to note this important change in the protocol. It is also not clear if cutting the patch into quarters would change the release properties. This presents a significant problem in the interpretation of this study.

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**Contact hypersensitivity to SDZ ENA 713 TDS in albino Guinea pigs. Modified Buehler method**

(Study Report 282071: \_\_\_\_\_  
commenced 29 OCT 1990; GLP OECD, EPA; QA; SDZ ENA 713 TDS Batch  
#W0730890)

b(4)

**Key Points**

- No skin reactions were observed in guinea pigs upon challenge with SDZ ENA 713 patch (4 cm<sup>2</sup>) or placebo patch (4 cm<sup>2</sup>), 2 weeks following a 3-wk once weekly induction period.

**Methods**

Iba: GOHI guinea pigs (N=10F Placebo, and 20 F Drug); 8 wks old; 317-333 g) were treated with one Placebo patch (4 cm<sup>2</sup>) or one SDZ ENA 713 TDS patch (4 cm<sup>2</sup>), applied to the shaved dorsum and covered by a \_\_\_\_\_ and occluded with a rubber dental dam, pulled snug on each side of the animal and secured with one or more large size clip(s) on each side of the restrainer. Patches were removed after 6 hrs. During the 3-wk induction phase, animals were once per week. Two weeks after the 3<sup>rd</sup> induction application, the placebo and test animals were challenged for 6 hrs with both a test article and a placebo patch (one on each flank). Dermal reactions were assessed 24 and 48 hrs after removal of the challenge patches.

b(4)

**Results**

No skin reactions were observed in any animals.

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**Contact hypersensitivity in albino Guinea pigs modified Buehler method**

(Study Report 605891)

Dosing commenced 11 SEP 1995; GLP FDA 1991; QA; SDZ ENA 713 TDS Batch #X1350595, Purity 100.5%)

b(4)

Key Points

- 24-hr treatments with SDZ ENA 713 patch (18 mg/10 cm<sup>2</sup>) or placebo patch (10 cm<sup>2</sup>) resulted in slight to moderate erythema in both groups after the 3 induction treatments, but no skin reactions were observed following the sensitization treatment.
- 1/20 SDZ ENA 713 patch animals was found dead on Day 11 (after the second induction treatment on Day 8), with sedation, ruffled fur, and slight dyspnea observed on Day 10.

Methods

Iba: GOHI guinea pigs (N=10F Placebo, and 20 F Drug); 6-8 wks old; 325-450 g) were pretreated with 10% sodium-lauryl-sulfate in paraffinum perliquidum, and treated with one Placebo patch (18 mg/10 cm<sup>2</sup>) or one SDZ ENA 713 TDS patch (10 cm<sup>2</sup>), applied to the shaved dorsum and covered by an elastic plaster, which was wrapped around the trunk of the animal and secured with an impervious adhesive tape. Patches were removed after 24 hrs. During the 3-wk induction phase, animals were once per week. Two weeks after the 3<sup>rd</sup> induction application, the placebo and test animals were challenged for 6 hrs with both a test article and a placebo patch (one on each flank). Dermal reactions were assessed 24 hrs after each induction treatment, and 24 hrs and 48 hrs after removal of the challenge patches.

Results

1/20 SDZ ENA 713 patch animals was found dead on Day 11 after the second induction treatment on Day 8. This animal had shown the following signs on Day 10: sedation, ruffled fur, and slight dyspnea. The study author considered this death "unrelated to treatment since no clinical signs were observed in any other animal during the study." (Page 24 of Study Report) This reviewer does not concur, base on spontaneous deaths at the same dose only in the drug-treated group in a similar study.

Slight to moderate erythema was observed after each induction treatment in both SDZ ENA 713 and placebo groups. (See tables on following pages)

No skin reactions were observed following challenge treatments.

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**INDUCTION WEEK 1 / test day 1 - control group**Test article: SDZ ENA 713 Transdermal systems (TDS) placebo/10cm<sup>2</sup>

Animal number females	433	434	435	436	437	438	439	440	441	442
Erythema	1*	0	0	0	0	1*	0	1*	0	0
Oedema	0	0	0	0	0	0	0	0	0	0

**INDUCTION WEEK 2 / test day 8 - control group**Test article: SDZ ENA 713 Transdermal systems (TDS) placebo/10cm<sup>2</sup>

Animal number females	433	434	435	436	437	438	439	440	441	442
Erythema	0	1	0	0	0	0	0	0	1	1
Oedema	0	0	0	0	0	0	0	0	0	0

**INDUCTION WEEK 3 / test day 15 - control group**Test article: SDZ ENA 713 Transdermal systems (TDS) placebo/10cm<sup>2</sup>

Animal number females	433	434	435	436	437	438	439	440	441	442
Erythema	*	1	1	0	0	*	0	*	1	1*
Oedema	0	0	0	0	0	0	0	0	0	0

\* = Encrustation

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**INDUCTION WEEK 1 / test day 1 - test group**

Test article: SDZ ENA 713 Transdermal systems (TDS) 18 mg/10 cm<sup>2</sup>

Animal number females	443	444	445	446	447	448	449	450	451	452
Erythema	0	1*	0	1*	0	2*	1*	1*	0	2*
Oedema	0	0	0	0	0	0	0	0	0	0

Animal number females	453	454	455	456	457	458	459	460	461	462
Erythema	1*	0	0	0	1*	1*	1*	1*	0	0
Oedema	0	0	0	0	0	0	0	0	0	0

**INDUCTION WEEK 2 / test day 8 - test group**

Test article: SDZ ENA 713 Transdermal systems (TDS) 18 mg/10 cm<sup>2</sup>

Animal number females	443	444	445	446	447	448	449	450	451	452
Erythema	1*	1*	0	1*	0	1*	1*	1	1*	1
Oedema	0	0	0	0	0	0	0	0	0	0

Animal number females	453	454	455	456	457	458	459	460	461	462
Erythema	0	*	*	1*	0	*	0	1*	*	0
Oedema	0	0	0	0	0	0	0	0	0	0

**INDUCTION WEEK 3 / test day 15 - test group**

Test article: SDZ ENA 713 Transdermal systems (TDS) 18 mg/10 cm<sup>2</sup>

Animal number females	443	444	445	446	447	448	449	450	451	452
Erythema	*	1	1*	1*	1	1*	-	1	1*	1
Oedema	0	0	0	0	0	0	-	0	0	0

Animal number females	453	454	455	456	457	458	459	460	461	462
Erythema	1	1	*	1	0	1*	1	1	1*	1*
Oedema	0	0	0	0	0	0	0	0	0	0

- = Was found dead on test day 11

\* = Encrustation

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**Contact hypersensitivity in albino Guinea pigs modified Buehler method**

(Study Report 646694: \_\_\_\_\_ Dosing commenced 22 JAN 1997; GLP FDA 1991; QA; SDZ ENA 713 TDS Batch #2409-1; this batch differs from the to-be-marketed patch in containing \_\_\_\_\_)

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**b(4)**Key Points

- Induction of guinea pigs with the full-sized SDZ ENA 713 TDS patch (18 mg/10 cm<sup>2</sup>) once weekly for 2 weeks and a quarter-sized patch the third week did not result in sensitization when challenged with a quarter-sized SDZ ENA 713 TDS patch 2 weeks after the 3<sup>rd</sup> induction treatment; no skin reactions were observed.
- Slight to moderate erythema was observed after SDZ ENA 713 patch treatment after the second induction treatment.
- 3/20 animals died after the second induction treatment due to drug-related toxicity.

Methods

Ibm: Dunkin-Hartley guinea pigs (N=10M Control, and 20M Drug); 6-7 wks old; 324-466 g) were treated with one SDZ ENA 713 TDS patch (18 mg/10 cm<sup>2</sup>), applied to the shaved dorsum (pretreated with 10% sodium-lauryl-sulfate in paraffinum perliquidum during the sensitization induction phase) and covered by an elastic plaster which was wrapped around the trunk of the animal and secured with an impervious adhesive tape. Patches were removed after 24 hrs. During the 3-wk induction phase, one treatment was given per week. The third induction treatment was performed with quarter-sized patches due to drug-related deaths in 3/20 animals after the second induction treatment. Controls were not treated during the induction period. Two weeks after the 3<sup>rd</sup> induction application, the test and control animals were challenged by application of a test article quarter-sized patch for 24 hrs as described above. Dermal reactions were assessed at 24 hrs after removal of the induction patches, and at 24 and 48 hrs after removal of the challenge patches.

Results

After the second induction treatment on Day 8, 3/20 drug-treated animals were found dead (2 on Day 9, 1 on Day 10), attributed to pharmacological activity of the test substance (signs in one animal included tremor, ventral recumbency, and ruffled fur; necropsy showed black-brown contents in the dilated cecum, lungs with dark red or red-brown foci, red brown contents in jejunum and tan discolored liver).

No skin reactions were observed after the first induction treatment. Slight to moderate erythema was observed in 16/17 drug-treated animals after the second treatment, along with fissures and scales. Only 1/17 animals showed erythema after the third induction treatment.

No animals induced with the SDZ ENA 713 TDS patch showed a skin reaction to challenge with the test-article patch, and only 1/10 control animals (uninduced) showed a very slight erythema in response to challenge with the SDZ ENA 713 TDS patch.

Therefore, under the conditions tested, the ENA 713 TDS patch was considered not to be a sensitizer.

### INDUCTION WEEK 1 / test day 1 - test group

Test article: SDZ ENA 713 TDS: COMPOSITION 1:2409-1

Animal number Males	711	712	713	714	715	716	717	718	719	720
Erythema	0	0	0	0	0	0	0	0	0	0
Oedema	0	0	0	0	0	0	0	0	0	0

Animal number Males	721	722	723	724	725	726	727	728	729	730
Erythema	0	0	0	0	0	0	0	0	0	0
Oedema	0	0	0	0	0	0	0	0	0	0

### INDUCTION WEEK 2 / test day 8 - test group

Test article: SDZ ENA 713 TDS: COMPOSITION 1:2409-1

Animal number Males	711	712	713	714	715	716	717	718	719	720
Erythema	1	1	0	1	2	2	1	1	1	2
Oedema	0	0	0	0	0	0	0	0	0	0

Animal number Males	721	722	723	724	725	726	727	728	729	730
Erythema	exitus	1	2	exitus	1	exitus	2	1	1	1
Oedema	exitus	0	0	exitus	0	exitus	0	0	0	0

### INDUCTION WEEK 3 / test day 15 - test group

Test article: SDZ ENA 713 TDS: COMPOSITION 1:2409-1

Animal number Males	711	712	713	714	715	716	717	718	719	720
Erythema	0	0	0	0	0	0	0	0	0	0
Oedema	0	0	0	0	0	0	0	0	0	0

Animal number Males	721	722	723	724	725	726	727	728	729	730
Erythema	exitus	0	0	exitus	0	exitus	0	0	1	0
Oedema	exitus	0	0	exitus	0	exitus	0	0	0	0

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**Contact hypersensitivity in albino Guinea pigs modified Buehler method**  
(Study Report 646705. \_\_\_\_\_ Dosing commenced 22 JAN 1997; GLP FDA 1991; QA; SDZ ENA 713 TDS Batch #2415-1; this batch differs from the to-be-marketed patch in containing: \_\_\_\_\_)

b(4)

#### Key Points

- Induction of guinea pigs with the full-sized SDZ ENA 713 TDS patch (18 mg/10 cm<sup>2</sup>) once weekly for 2 weeks and a quarter-sized patch the third week did not result in sensitization when challenged with a quarter-sized SDZ ENA 713 TDS patch 2 weeks after the 3<sup>rd</sup> induction treatment; no skin reactions were observed.
- Slight to moderate erythema was observed after SDZ ENA 713 patch treatment after the second and third induction treatments.
- 5/20 animals died after the second or third induction treatments due to drug-related toxicity.

#### Methods

Dunkin-Hartley guinea pigs (N=10M Control, and 20M Drug); 6-7 wks old; 325-451 g) were treated with one SDZ ENA 713 TDS patch (18 mg/10 cm<sup>2</sup>), applied to the shaved dorsum (pretreated with 10% sodium-lauryl-sulfate in paraffinum perliquidum during the sensitization induction phase) and covered by an elastic plaster which was wrapped around the trunk of the animal and secured with an impervious adhesive tape. Patches were removed after 24 hrs. During the 3-wk induction phase, one treatment was given per week. The third induction treatment was performed with quarter-sized patches due to drug-related deaths in 5/20 animals after the second or third induction treatment. Controls were not treated during the induction period. Two weeks after the 3<sup>rd</sup> induction application, the test and control animals were challenged by application of a test article quarter-sized patch for 24 hrs as described above. Dermal reactions were assessed at 24 hrs after removal of the induction patches, and at 24 and 48 hrs after removal of the challenge patches.

#### Results

After the second (Day 8) or third (Day 15) induction treatments, 5/20 drug-treated animals were found dead (Days 10, 20, 21, or 22), attributed to pharmacological activity of the test substance (necropsy showed liquid contents in the dilated stomach, black-brown contents in the dilated cecum, lungs with dark red foci, and tan discolored liver).

No skin reactions were observed after the first induction treatment. Slight to moderate erythema was observed in 14/19 drug-treated animals after the second treatment (along with fissures and scales) and in 5/19 animals after the third induction treatment.

No animals in the group induced with the SDZ ENA 713 TDS patch or the control group showed a skin reaction to challenge with the test-article patch. Therefore, under the conditions tested, the ENA 713 TDS patch was considered not to be a sensitizer.

**INDUCTION WEEK 1 / test day 1 - test group**

Test article: SDZ ENA 713 TDS: COMPOSITION 2:2415-1

Animal number Males	279	280	281	282	283	284	285	286	287	288
Erythema	0	0	0	0	0	0	0	0	0	0
Oedema	0	0	0	0	0	0	0	0	0	0

Animal number Males	289	290	291	292	293	294	295	296	297	298
Erythema	0	0	0	0	0	0	0	0	0	0
Oedema	0	0	0	0	0	0	0	0	0	0

**INDUCTION WEEK 2 / test day 8 - test group**

Test article: SDZ ENA 713 TDS: COMPOSITION 2:2415-1

Animal number Males	279	280	281	282	283	284	285	286	287	288
Erythema	1	2	exitus	1	1	1	1	1	1	2
Oedema	0	0	exitus	0	0	0	0	0	0	0

Animal number Males	289	290	291	292	293	294	295	296	297	298
Erythema	0	0	0	0	1	1	0	1	1	1
Oedema	0	0	0	0	0	0	0	0	0	0

**INDUCTION WEEK 3 / test day 15 - test group**

Test article: SDZ ENA 713 TDS: COMPOSITION 2:2415-1

Animal number Males	279	280	281	282	283	284	285	286	287	288
Erythema	0	0	exitus	0	1	0	1	0	0	0
Oedema	0	0	exitus	0	0	0	0	0	0	0

Animal number Males	289	290	291	292	293	294	295	296	297	298
Erythema	0	1	0	0	0	0	0	1	1	0
Oedema	0	0	0	0	0	0	0	0	0	0

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**Contact hypersensitivity in albino Guinea pigs modified Buehler method**

(Study Report 646716; \_\_\_\_\_ Dosing commenced 22 JAN 1997; GLP FDA 1991; QA; SDZ ENA 713 TDS Batch #2421-1; this batch differs from the to-be-marketed patch in containing \_\_\_\_\_)

**b(4)****Key Points**

- Induction of guinea pigs with the full-sized SDZ ENA 713 TDS patch (18 mg/10 cm<sup>2</sup>) once weekly for 2 weeks and a quarter-sized patch the third week did not result in sensitization when challenged with a quarter-sized SDZ ENA 713 TDS patch 2 weeks after the 3<sup>rd</sup> induction treatment; slight erythema was observed in only 1/13 treated animals and in 1/10 control animals that had not been induced.
- Slight to moderate erythema was observed after SDZ ENA 713 patch treatment after the second and third induction treatments.
- 7/20 animals died after the second or third induction treatments due to drug-related toxicity.

**Methods**

Dunkin-Hartley guinea pigs (N=10M Control, and 20M Drug); 6-7 wks old; 323-441 g) were treated with one SDZ ENA 713 TDS patch (18 mg/10 cm<sup>2</sup>), applied to the shaved dorsum (pretreated with 10% sodium-lauryl-sulfate in paraffinum perliquidum during the sensitization induction phase) and covered by an elastic plaster which was wrapped around the trunk of the animal and secured with an impervious adhesive tape. Patches were removed after 24 hrs. During the 3-wk induction phase, one treatment was given per week. The third induction treatment was performed with quarter-sized patches due to drug-related deaths in 7/20 animals after the second or third induction treatment. Controls were not treated during the induction period. Two weeks after the 3<sup>rd</sup> induction application, the test and control animals were challenged by application of a test article quarter-sized patch for 24 hrs as described above. Dermal reactions were assessed at 24 hrs after removal of the induction patches, and at 24 and 48 hrs after removal of the challenge patches.

**Results**

After the second (Day 8) or third (Day 15) induction treatments, 7/20 drug-treated animals were found dead (Days 9, 12, 20, 21, 23, or 28), attributed to pharmacological activity of the test substance (necropsy showed stomach distended with gas, thickened and dark red discolored mucosa in stomach with liquid contents, black-brown contents in the undilated cecum distended with gas, incompletely collapsed lungs with several or isolated dark red foci, thickened mucosa, intussuscepted and dilated colon, and advanced autolysis).

No skin reactions were observed after the first induction treatment. Slight to moderate erythema was observed in 10/19 drug-treated animals after the second treatment (along with fissures and scales) and in 4/18 animals after the third induction treatment.

Only 1/13 in the treatment group and 1/10 in the control group showed a skin reaction (very slight erythema) in response to challenge with the test-article patch. Therefore, under the conditions tested, the ENA 713 TDS patch was considered not to be a sensitizer.

#### INDUCTION WEEK 1 / test day 1 - test group

Test article: SDZ ENA 713 TDS: COMPOSITION 3:2421-1

Animal number Males	871	872	873	874	875	876	877	878	879	880
Erythema	0	0	0	0	0	0	0	0	0	0
Oedema	0	0	0	0	0	0	0	0	0	0

Animal number Males	881	882	883	884	885	886	887	888	889	890
Erythema	0	0	0	0	0	0	0	0	0	0
Oedema	0	0	0	0	0	0	0	0	0	0

#### INDUCTION WEEK 2 / test day 8 - test group

Test article: SDZ ENA 713 TDS: COMPOSITION 3:2421-1

Animal number Males	871	872	873	874	875	876	877	878	879	880
Erythema	0	2	1	2	1	1	0	0	0	1
Oedema	0	0	0	0	0	0	0	0	0	0

Animal number Males	881	882	883	884	885	886	887	888	889	890
Erythema	1	0	exitus	0	2	0	1	1	0	0
Oedema	0	0	exitus	0	0	0	0	0	0	0

#### INDUCTION WEEK 3 / test day 15 - test group

Test article: SDZ ENA 713 TDS: COMPOSITION 3:2421-1

Animal number Males	871	872	873	874	875	876	877	878	879	880
Erythema	0	0	1	1	0	0	0	0	0	0
Oedema	0	0	0	0	0	0	0	0	0	0

Animal number Males	881	882	883	884	885	886	887	888	889	890
Erythema	0	0	exitus	0	1	1	0	0	0	exitus
Oedema	0	0	exitus	0	0	0	0	0	0	exitus

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**Contact hypersensitivity in albino Guinea pigs modified Buehler method**

(Study Report 646727; \_\_\_\_\_, Dosing commenced 22 JAN 1997; GLP FDA 1991; QA; SDZ ENA 713 TDS Batch #2427-1; this batch differs from the to-be-marketed patch in containing \_\_\_\_\_

**b(4)****Key Points**

- Induction of guinea pigs with the full-sized SDZ ENA 713 TDS patch (18 mg/10 cm<sup>2</sup>) once weekly for 2 weeks and a quarter-sized patch the third week resulted in sensitization when challenged with a quarter-sized SDZ ENA 713 TDS patch 2 weeks after the 3<sup>rd</sup> induction treatment; slight to moderate erythema was observed in 8/16 treated animals compared to 0/10 control animals that had not been induced.
- Slight to moderate erythema was observed after SDZ ENA 713 patch treatment after the second and third induction treatments.
- 4/20 animals died after the second or third induction treatments due to drug-related toxicity.

**Methods**

Dunkin-Hartley guinea pigs (N=10M Control, and 20M Drug); 6-7 wks old; 313-448 g) were treated with one SDZ ENA 713 TDS patch (18 mg/10 cm<sup>2</sup>), applied to the shaved dorsum (pretreated with 10% sodium-lauryl-sulfate in paraffinum perliquidum during the sensitization induction phase) and covered by an elastic plaster which was wrapped around the trunk of the animal and secured with an impervious adhesive tape. Patches were removed after 24 hrs. During the 3-wk induction phase, one treatment was given per week. The third induction treatment was performed with quarter-sized patches due to drug-related deaths in 4/20 animals after the second or third induction treatment. Controls were not treated during the induction period. Two weeks after the 3<sup>rd</sup> induction application, the test and control animals were challenged by application of a test article quarter-sized patch for 24 hrs as described above. Dermal reactions were assessed at 24 hrs after removal of the induction patches, and at 24 and 48 hrs after removal of the challenge patches.

**Results**

After the second (Day 8) or third (Day 15) induction treatments, 4/20 drug-treated animals were found dead (Days 9, 10, or 21), attributed to pharmacological activity of the test substance (one showed signs of tremor, ventral recumbency, and ruffled fur; necropsies showed dilation of stomach with liquid contents, black-brown contents in the dilated or undilated cecum, lungs with dark red foci, jejunum mucosa with dark red foci and left lateral lobe in the liver with gray white foci).

No skin reactions were observed after the first induction treatment. Slight to moderate erythema was observed in 15/17 drug-treated animals after the second treatment (along with fissures and scales) and in 12/17 animals after the third induction treatment.

Significant skin reactions (slight to moderate erythema) were observed in 8/16 animals in the treatment group compared to 0/10 in the control group. Therefore, under the conditions tested, the ENA 713 TDS patch was considered to be a sensitizer.

**INDUCTION WEEK 1 / test day 1 - test group**

Test article: SDZ ENA 713 TDS: COMPOSITION 4:2427-1

Animal number Males	841	842	843	844	845	846	847	848	849	850
Erythema	0	0	0	0	0	0	0	0	0	0
Oedema	0	0	0	0	0	0	0	0	0	0

Animal number Males	851	852	853	854	855	856	857	858	859	860
Erythema	0	0	0	0	0	0	0	0	0	0
Oedema	0	0	0	0	0	0	0	0	0	0

**INDUCTION WEEK 2 / test day 8 - test group**

Test article: SDZ ENA 713 TDS: COMPOSITION 4:2427-1

Animal number Males	841	842	843	844	845	846	847	848	849	850
Erythema	1	1	1	2	0	1	exitus	1	0	exitus
Oedema	0	0	0	0	0	0	exitus	0	0	exitus

Animal number Males	851	852	853	854	855	856	857	858	859	860
Erythema	1	2	1	1	1	2	1	exitus	1	1
Oedema	0	0	0	0	0	0	0	exitus	0	0

**INDUCTION WEEK 3 / test day 15 - test group**

Test article: SDZ ENA 713 TDS: COMPOSITION 4:2427-1

Animal number Males	841	842	843	844	845	846	847	848	849	850
Erythema	1	1	1	1	1	0	exitus	1	1	exitus
Oedema	0	0	0	0	0	0	exitus	0	0	exitus

Animal number Males	851	852	853	854	855	856	857	858	859	860
Erythema	0	1	1	0	0	2	1	exitus	0	1
Oedema	0	0	0	0	0	0	0	exitus	0	0

**CONTROL GROUP**

Challenge: SDZ ENA 713 TDS: COMPOSITION 4:2427-1

Animal number Males	831	832	833	834	835	836	837	838	839	840
Erythema 24-hours	0	0	0	0	0	0	0	0	0	0
48-hours	0	0	0	0	0	0	0	0	0	0
Oedema 24-hours	0	0	0	0	0	0	0	0	0	0
48-hours	0	0	0	0	0	0	0	0	0	0

**TEST GROUP**

Challenge: SDZ ENA 713 TDS: COMPOSITION 4:2427-1

Animal number Males	841	842	843	844	845	846	847	848	849	850
Erythema 24-hours	0	0	±	1	0	2	exitus	1	0	exitus
48-hours	0	0	0	1	0	2	exitus	1	0	exitus
Oedema 24-hours	0	0	0	0	0	0	exitus	0	0	exitus
48-hours	0	0	0	0	0	0	exitus	0	0	exitus

Animal number Males	851	852	853	854	855	856	857	858	859	860
Erythema 24-hours	2	1	0	0	1	exitus	1	exitus	0	1
48-hours	1	1	0	0	1	exitus	1	exitus	0	0
Oedema 24-hours	0	0	0	0	0	exitus	0	exitus	0	0
48-hours	0	0	0	0	0	exitus	0	exitus	0	0

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**Contact hypersensitivity in albino Guinea pigs modified Buehler method**

(Study Report 646738; \_\_\_\_\_, Dosing commenced 22 JAN 1997; GLP FDA 1991; QA; SDZ ENA 713 TDS Batch #2437-1)

**b(4)**Key Points

- Induction of guinea pigs with the full-sized SDZ ENA 713 TDS patch (18 mg/10 cm<sup>2</sup>) once weekly for 2 weeks and a quarter-sized patch the third week did not result in sensitization when challenged with a quarter-sized SDZ ENA 713 TDS patch 2 weeks after the 3<sup>rd</sup> induction treatment; no skin reactions were seen.
- Slight to severe erythema was observed after SDZ ENA 713 patch treatment after the second and third induction treatments.
- 8/20 animals died after the second or third induction treatments due to drug-related toxicity.

Methods

Dunkin-Hartley guinea pigs (N=10M Control, and 20M Drug); 6-7 wks old; 314-430 g) were treated with one SDZ ENA 713 TDS patch (18 mg/10 cm<sup>2</sup>), applied to the shaved dorsum (pretreated with 10% sodium-lauryl-sulfate in paraffinum perliquidum during the sensitization induction phase) and covered by an elastic plaster which was wrapped around the trunk of the animal and secured with an impervious adhesive tape. Patches were removed after 24 hrs. During the 3-wk induction phase, one treatment was given per week. The third induction treatment was performed with quarter-sized patches due to drug-related deaths in 8/20 animals after the second or third induction treatment. Controls were not treated during the induction period. Two weeks after the 3<sup>rd</sup> induction application, the test and control animals were challenged by application of a test article quarter-sized patch for 24 hrs as described above. Dermal reactions were assessed at 24 hrs after removal of the induction patches, and at 24 and 48 hrs after removal of the challenge patches.

Results

After the second (Day 8) or third (Day 15) induction treatments, 8/20 drug-treated animals were found dead (Days 9, 12, 20, 21, 23, or 28), attributed to pharmacological activity of the test substance (four showed signs of tremor, ventral recumbency, and/or ruffled fur; necropsies showed dilated stomach with liquid contents, black-brown or liquid contents in the dilated or undilated cecum, not collapsed lungs ± dark red foci, abdominal cavity containing watery clear fluid and tan discolored liver).

No skin reactions were observed after the first induction treatment. Slight to severe erythema was observed in 11/13 drug-treated animals after the second treatment (along with fissures and scales) and slight to moderate erythema was seen in 8/12 animals after the third induction treatment.

No skin reactions were observed in response to challenge with the test-article patch. Therefore, under the conditions tested, the ENA 713 TDS patch was considered not to be a sensitizer.

**INDUCTION WEEK 1 / test day 1 - test group**

Test article: SDZ ENA 713 TDS: COMPOSITION 5:2437-1

Animal number Males	811	812	813	814	815	816	817	818	819	820
Erythema	0	0	0	0	0	0	0	0	0	0
Oedema	0	0	0	0	0	0	0	0	0	0

Animal number Males	821	822	823	824	825	826	827	828	829	830
Erythema	0	0	0	0	0	0	0	0	0	0
Oedema	0	0	0	0	0	0	0	0	0	0

**INDUCTION WEEK 2 / test day 8 - test group**

Test article: SDZ ENA 713 TDS: COMPOSITION 5:2437-1

Animal number Males	811	812	813	814	815	816	817	818	819	820
Erythema	1	1	exitus	exitus	exitus	exitus	exitus	2	0	exitus
Oedema	0	0	exitus	exitus	exitus	exitus	exitus	0	0	exitus

Animal number Males	821	822	823	824	825	826	827	828	829	830
Erythema	2	1	1	1	2	1	0	exitus	1	3
Oedema	0	0	0	0	0	0	0	exitus	0	0

**INDUCTION WEEK 3 / test day 15 - test group**

Test article: SDZ ENA 713 TDS: COMPOSITION 5:2437-1

Animal number Males	811	812	813	814	815	816	817	818	819	820
Erythema	0	1	exitus	exitus	exitus	exitus	exitus	1	0	exitus
Oedema	0	0	exitus	exitus	exitus	exitus	exitus	0	0	exitus

Animal number Males	821	822	823	824	825	826	827	828	829	830
Erythema	1	0	0	1	1	1	exitus	exitus	1	1
Oedema	0	0	0	0	0	0	exitus	exitus	0	0

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**Assessment of contact hypersensitivity to ENA713 in the albino guinea pig (Buehler test)**

(Study Report 0420009-~~\_\_\_\_\_~~ Project #399217: ~~\_\_\_\_\_~~  
~~\_\_\_\_\_~~ Dosing commenced 11 FEB 2004; GLP OECD, EPA; QA; SDZ ENA 713  
TDS Batch #8/22061/02)

b(4)

**Key Points**

- Application of the SDZ ENA 713 patch (9 mg/5 cm<sup>2</sup>) for 6 hrs to guinea pigs resulted in slight to moderate erythema during the induction phase in 12/20; placebo patches (5 cm<sup>2</sup>) induced slight to well-defined erythema in 5/10 animals.
- At 24 hrs after the challenge treatment, grade 1-2 erythema was observed in 9/20 ENA 713/ENA 713, 4/20 ENA 713/placebo, 2/10 placebo/ENA 713, and 2/10 placebo/placebo animals (induction/challenge).
- At 48 hrs after the challenge treatment, discrete or patchy erythema was observed in 2/20 ENA 713/ENA 713, 1/20 ENA 713/placebo, 1/10 placebo/ENA 713, and 1/10 placebo/placebo animals.
- The observed sensitization rate of ~5-10% was attributed to the patch rather than to the drug substance, and the SDZ ENA 713 patch was considered a non-sensitizer.

**Methods**

Dunkin Hartley guinea pigs (N=10F Placebo, and 20 F Drug); 5 wks old; 330-405 g) were treated with one Placebo patch (5 cm<sup>2</sup>) or one SDZ ENA 713 TDS patch (9 mg/5 cm<sup>2</sup>), applied to the shaved dorsum and covered by Patch Test Plasters, held in place with Micropore tape and wrapped with a Coban elastic bandage. Patches were removed after 6 hrs. During the 3-wk induction phase, animals were treated on Days 1, 8, and 15. Two weeks after the 3<sup>rd</sup> induction application, the placebo and test animals were challenged for 6 hrs with both a test article and a placebo patch (one on each flank). Dermal reactions were assessed 24 and 48 hrs after removal of the challenge patches.

**Results**

No changes in clinical signs or body weights were observed.

After the third induction treatment, erythema was noted in 12/20 ENA 713 patch animals (slight in 7, well-defined to moderate in 5) and in 5/10 placebo patch animals (all slight). Thus, the ENA 713 patches induced irritation at about the same frequency as the placebo patches, but slightly increased the severity.

At 24 hrs after removal of the challenge patches, discrete or patchy (grade 1) to moderate and confluent (grade 2) erythema was observed in 9/20 animals induced with ENA 713 patches and challenged with ENA 713 patches; in 4/20 animals induced with ENA 713 patches and challenged with placebo patches; in 2/10 animals induced with placebo patches and challenged with ENA 713 patches; and in 2/10 animals induced with placebo patches and challenged with placebo patches. Seven of the reactions noted above were no longer present at 48 hrs post-challenge, and (according to the study authors) could be indicative of irritation rather than sensitization.

At 48 hrs, after removal of the challenge patches, discrete or patchy erythema was observed in 2/20, 1/20, 1/10, and 1/10, respectively, in the groups described above. These reactions were indicative of slight sensitization attributed to the patch itself, rather than to the test substance. Based on the observed sensitization rate of 5% for the ENA 713 patch, this patch should not be classified as a skin sensitizer according to the OECD Harmonized Integrated Hazard Classification System for Human Health and Environmental Effects of Chemical Substances (OECD, 1998).

The number of animals presenting with erythema of grade 1 or 2 after challenge is summarized as follows:

Group	Induction	Challenge	No. of affected animals	
			24 hours after challenge	48 hours after challenge
1 (control)	placebo	placebo	2/10	1/20
		test item	2/10	1/20
2 (test item)	test item	placebo	4/20	1/20
		test item	9/20	2/20

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**Delayed contact hypersensitivity to SDZ 212-713 hta in albino guinea pigs. The Maurer optimization test.**

(Study Report 214380; \_\_\_\_\_ Dosing commenced 15 AUG 1988; GLP OECD 1981; QA; SDZ 212-713 hta salt Batch #88902)

**b(4)**Key Points

- No positive skin reactions were observed in control or test-article treated animals after the first or second challenge application.
- SDZ 212-713 hta was considered to be a non-sensitizer.

Methods

Dunkin-Hartley guinea pigs (N=12/sex/group); 8-9 wks old; 291-402 g) were induced by intradermal injection of 0.1 mL of 0.1% test article in saline into the shaven flank and back on Monday and into the back only on Wednesday and Friday during Week 1; and intradermal injection of 0.1% test article in saline mixed 1:1 (v/v) with Freund's Complete Adjuvant (FCA) into the nuchal skin on Monday, Wednesday, and Friday of Weeks 2 and 3. Control animals received similar injection containing vehicle alone.

Challenge 1, performed 13 days after the last induction dose, consisted of intradermal injection of 0.1 mL of 0.1% test article in saline into an area of untreated flank. Control animals received similar injections of vehicle alone.

Challenge 2, performed 13 days after Challenge 1, consisted of application of a 2 x 2 cm filter paper patch impregnated with 30% test article in Vaseline to an untreated shaven skin area of the right flank of both treated and control groups. The patch was anchored by an occlusive dressing for 24 hrs. The left flank of both treated and control groups was treated similarly with patches impregnated with Vaseline alone.

Dermal reactions were assessed 24 hrs after Week 1 induction injections, 24 hrs after Challenge 1 injections, and 24 hrs after removal of the patch in Challenge 2.

Results

No positive skin reactions were observed in control or test-article treated animals after the first or second challenge application. Control F #935 died spontaneously on Day 7; necropsy revealed dark-red discoloration of lung.

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**Contact hypersensitivity in albino Guinea pigs maximization-test**

(Study Report 622631: \_\_\_\_\_ Dosing commenced 09 APR 1996; GLP FDA 1991; QA; SDZ ENA 713 liquid Batch #95703, Purity 99.5%)

b(4)

**Key Points**

- No skin reactions were observed after epidermal induction with the test article or the vehicle, or following the epidermal challenge with the test article or vehicle.

**Methods**

Iba: GOHI guinea pigs (N=10F Placebo, and 20 F Drug); 7-9 wks old; 323-426 g) were induced by administration of 3 pairs of intradermal injections on test day 1 (0.1 mL/site) at the borders of a 4 x 6 cm area within the 6 x 8 cm area of dorsal skin clipped free of hair: 1) 1:1 (v/v) Freund's Complete Adjuvant (FCA) and saline; 2) 0.5% SDZ ENA 713 in ethanol/water (1:1); and 3) 0.5% SDZ ENA 713 in 1:1 FCA and saline. Control animals were induced with similarly paired intradermal injections: 1) 1:1 (v/v) FCA and saline; 2) ethanol/water (1:1); and 3) 1:1 (w/w) mixture of ethanol/water (1:1) in 1:1 (v/v) mixture of FCA and saline. Epicutaneous inductions were performed on Day 8 by applying a 2 x 4 cm patch of filter paper saturated with 30% SDZ ENA 713 in ethanol/water (1:1) to the previously injected skin area, and covering with an occlusive dressing for 48 hrs (aluminum foil firmly secured with an elastic plaster wrapped around the trunk and secured with impervious adhesive tape). Controls were treated similarly, except the filter paper patch was saturated with ethanol/water (1:1) only. Dermal reactions were assessed 24 and 48 hrs after the epicutaneous induction treatment.

Challenge tests performed two weeks after the epidermal induction application (Day 22) consisted of application of two patches of 2 x 2 cm filter paper: one saturated with 30% SDZ ENA 713 in ethanol/water (1:1) (left flank), and the other saturated with just ethanol/water (1:1) (right flank). Patches were secured and wrapped as before, and left in place for 24 hrs. Test-article and Control groups were treated similarly. Dermal reactions were assessed 24 and 48 hrs after the epicutaneous challenge treatment.

**Results**

No skin reactions were observed after epidermal induction with the test article or the vehicle, or following the epidermal challenge with the test article or vehicle.

2/10 control animals were found dead on Days 9 and 11, and 2/20 test article animals were found dead on Day 10 and 23. No clear relation to treatment was found upon necropsy.

Separate positive control studies with 2-mercaptobenzothiazole and alpha-hexylcinnamaldehyde performed as expected using similar procedures.

**Primary eye irritation study in rabbits**

(Study Report 605777; ~~\_\_\_\_\_~~  
Dosing commenced 19 SEP 1995; GLP FDA 1991; QA; SDZ ENA 713 liquid Batch #94702, Purity 101.1%)

**b(4)****Key Points**

- Eye irritation could not be assessed due to spontaneous death of 3/3 rabbits within ~1 hr of treatment.

**Methods**

New Zealand White rabbits (N=1M, 2F; 15 wks old; 2.5-2.9 kg) were treated with 0.1 mL SDZ ENA 713 into the conjunctival sacs of the left eyes; the right eyes were left untreated. The eyelid was gently held closed for ~1 second after administration to insure retention of the test article.

**Results**

All 3 rabbits were found dead ~1 hr after dosing. No clinical signs were observed. Necropsy revealed bluish discoloration of the skin, moderate to severe ocular discharge and moderate conjunctival swelling in all 3 animals. Evidence of increased salivation was observed in 1/3. Eye irritation could not be assessed due to spontaneous death within 1 hr of treatment.

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**Primary eye irritation study in rabbits (low volume procedure)**

(Study Report 613135; \_\_\_\_\_)

Dosing commenced 08 JAN 1996; GLP FDA 1991; QA; SDZ ENA 713 liquid Batch #94702, Purity 99.9%)

b(4)

Key Points

- Clinical signs included slight to moderate tremor, impaired coordination, recumbency, and hyperreactivity to tactile stimulus, starting ~1 hr postdose.
- Eye reactions included miosis, moderate to marked lacrimation, loss of reactivity to light in the iris, and reddening and swelling of the conjunctivae starting ~1 hr postdose, and slight diffuse corneal opacities starting ~24 hrs postdose. All eyes were normal by 7 days postdose.
- The primary eye irritation score for SDZ ENA 713 at the dose of 10 uL was 3.44, which was classified as “not irritating” to the rabbit eye, according to commonly used criteria.

Methods

New Zealand White rabbits (N=1M, 2F; 15 wks old; 2.6-2.7 kg) were treated with 10 uL SDZ ENA 713 onto the cornea of the left eyes; the right eyes were left untreated. Eye examinations were conducted 1 hr, 24 hr, 48 hr, 72 hr, and 7 days after treatment. Clinical signs were noted 3 times on the first day, and daily thereafter. Body weights were recorded predose and on Day 7.

Results

All 3 rabbits showed slight to moderate tremor, impaired coordination, and recumbency ~1 hr after dosing; one animal was hyperreactive to tactile stimulus. At 2 hrs postdose, tremor was minimal to slight and coordination was impaired in 3/3; 1/3 showed extreme upright sitting position; and 2/3 showed normal posture. At 5 hrs postdose all clinical signs had abated except for very slight impairment of coordination in 1/3, which had disappeared by 24 hrs postdose.

Eye reactions observed in all animals at one hr postdose included miosis, moderate to marked lacrimation, loss of reactivity to light in the iris, and reddening (grade 2) and swelling (grade 3) of the conjunctivae. Reddening and swelling of the conjunctivae persisted at grades 1-2 through Day 3, but normalized by Day 7. Slight diffuse corneal opacities observed in all rabbits at 24 hrs postdose also persisted through Day 3, but normalized by Day 7. The primary eye irritation score for SDZ ENA 713 at the dose of 10 uL was 3.44, which was classified as “not irritating” to the rabbit eye, according to commonly used criteria.

### EYE IRRITATION SCORES

ANIMAL	SEX		CORNEA OPACITY	IRIS	CONJUNCTIVAE REDN. CHEM.	CUMUL. SCORE	MEAN CUMUL. SCORE
<b>1 HOUR</b>							
25	M	NOT RINSED	0	2 *	2 *	3 *	7
26	F	NOT RINSED	0	2 *	2 *	3 *	7
27	F	NOT RINSED	0	2 *	2 *	3 *	7
							7.00
<b>24 HOURS</b>							
25	M	NOT RINSED	1 *	0	1	2 *	4
26	F	NOT RINSED	1 *	0	1	2 *	4
27	F	NOT RINSED	1 *	1 *	1	2 *	5
							4.33
<b>48 HOURS</b>							
25	M	NOT RINSED	1 *	0	1	1	3
26	F	NOT RINSED	1 *	0	1	1	3
27	F	NOT RINSED	1 *	0	1	1	3
							3.00
<b>72 HOURS</b>							
25	M	NOT RINSED	1 *	0	1	1	3
26	F	NOT RINSED	1 *	0	1	1	3
27	F	NOT RINSED	1 *	0	1	1	3
							3.00
<b>7 DAYS</b>							
25	M	NOT RINSED	0	0	0	0	0
26	F	NOT RINSED	0	0	0	0	0
27	F	NOT RINSED	0	0	0	0	0
							0.00

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### 2.6.6.8 Special toxicology studies

#### SDZ ENA 713 dermal patches: Phototoxicity study in the Guinea-Pig

(Study report 95/SPM081/1368; ~~\_\_\_\_\_~~ Dosing commenced 13 NOV 1995; GLP UK 1989, OECD 1981; QA; SDZ ENA 713 TDS Batch #X135 0595)

b(4)

#### Key Points

- No phototoxicity was demonstrated in guinea pigs exposed to UV-A radiation for 90 minutes following a 30 minute dermal application of a SDZ ENA 713 patch.

#### Methods

Dunkin-Hartley guinea pigs (3/sex/group) were each treated with two SDZ ENA 713 TDS patches (4.5 mg/2.25 cm<sup>2</sup>; 1.5 x 1.5 cm, cut from standard 18 mg/10 cm<sup>2</sup> patches) or two placebo patches (2.25 cm<sup>2</sup>; 1.5 x 1.5 cm, cut from standard 10 cm<sup>2</sup> placebo patches), applied to the shaved dorsum for 30 minutes. One site on each animal was then covered by a UV opaque plastic mask, and the back of the animal was exposed to UV radiation in the UV-A waveband at 2.5-2.6 mW/cm<sup>2</sup> for one and a half hours. A positive control group was treated similarly after direct application of 0.05 mL of 0.01% w/v 8-methoxypsoralen in aqueous 70% v/v ethanol to the 1.5 x 1.5 cm test site, instead of test-article or placebo patches. Dermal reactions were evaluated 1 hr, 24 hrs, 48 hrs, and 7 days after treatment.

#### Results

No dermal reaction was observed at the irradiated or non-irradiated sites of the animals treated with SDZ ENA 713 patches or placebo patches.

The irradiated site on the positive control animals showed slight edema at 24 hrs, and slight erythema at 24 and 48 hrs post-treatment; and slight erythema, eschar formation, and exfoliation at 7 days. The non-irradiated site showed slight erythema at 24 and 48 hrs in one positive control animal.

SDZ ENA 713 dermal patches did not elicit a phototoxic response under the conditions tested.

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### 2.6.6.9 Discussion and Conclusions

Toxicology studies submitted to support NDA 22-083 for ENA713D (rivastigmine transdermal system, Exelon Patch, or SDZ ENA 713 patches) included repeat-dose general toxicology studies in mice, rats, rabbits, and minipigs; a 98-99-week dermal carcinogenicity study in mice; primary irritation studies in rabbits; contact hypersensitivity studies in guinea pigs; primary eye irritation studies in rabbits; and a phototoxicity study in rabbits.

Mice treated once daily with rivastigmine in 50% ethanol via dermal application directly onto the shaved back with a pipette tip for up to 13 weeks demonstrated dose-dependent clinical signs expected for cholinergic drugs: underactivity, piloerection, body tremors, irregular breathing, unusual posture, and/or yawning. No skin reactions were noted at the application site.

Similarly, rats treated once daily with rivastigmine in 50% ethanol via dermal application directly onto the shaved back with a pipette tip for 2-4 weeks showed dose-dependent twitching, tremors, lacrimation, and salivation, with correlating histopathology changes in salivary glands attributed to enhanced cholinergic stimulation. No signs of local toxicity were observed.

Rabbits treated once daily with ENA713D applied to the same site on the shaved dorsal surface for 5 days (up to 8 cm<sup>2</sup>/animal) to 4 weeks (up to 5 cm<sup>2</sup>/animal) showed very slight to well-defined erythema and edema at the application site, accompanied by histopathological findings consistent with minor irritation (mononuclear and inflammatory cell infiltration, dermal hyperplasia, akantosis, fibroplasia, and necrosis), attributed to the mechanical injury caused by repeated removal of the strongly adhesive patches. In 2 of the 3 rabbit studies, placebo patches did not induce irritation, but in the third (with histopathology) placebo and drug-containing patches induced roughly similar incidence and severity of erythema, edema, scaling, bruising, and scabbing. No systemic toxicity was observed in rabbits.

Dermal toxicity studies in minipigs treated with ENA713D or placebo patch for 2-4 weeks revealed that severe erythema (necessitating changing the application site and/or humane sacrifice) occurred, variably, in a few placebo and drug-treated animals by Day 9 when patches were applied to the same site every day or every other day. Most animals had slight to no erythema in these studies. The severity of the erythema correlated with the severity of dermatitis observed in the histopathological evaluation of the test site. No systemic toxicities were observed, even at the highest dose tested of 216 mg/animal/day (twelve 10 cm<sup>2</sup> patches or six 20 cm<sup>2</sup> patches). Although one or two individual placebo-treated animals showed moderate to severe erythema in the 2-wk and the first 4-wk minipig studies, in general the drug-treated patches appeared to be slightly more irritating to minipig skin compared to placebo patches.

In the pivotal 26-wk dermal minipig study, treatment with one or two 18 mg/10 cm<sup>2</sup> patches per day rotated such that each skin site was re-used every 12<sup>th</sup> day (or every 6<sup>th</sup> day in a second HD group) resulted in very slight to well-defined erythema at the application site from Wk 3 onward in drug-treated groups only. The frequency and severity of the erythema observed increased slightly with the application of 2 patches/day vs. 1 patch/day, and when sites were re-used every 6<sup>th</sup> day vs. every 12<sup>th</sup> day. However, no correlating histopathology changes were noted in the 26-wk study, and no other treatment-related changes were observed. Therefore, dosing in minipigs was limited by the number of skin sites to rotate patches among rather than by systemic toxicity. The mean fraction of drug delivered from the patches over the 24-hr application period was 40-67% in minipig (average of all 4 repeat-dose studies), independent of dose or sex.

Treatment of minipigs by oral gavage at the high dose of 6 mg/kg/day SDZ ENA 713 for 4 weeks resulted in frequent, transient, slight to moderate tremors, slight lateral recumbency, and slight occasional decreased activity and salivation. No other evidence of toxicity was noted. It is interesting to note that dermal administration of SDZ ENA 713 did not induce clinical signs even at exposures greatly exceeding those associated with cholinergic signs at the high oral dose of 6 mg/kg/day described above (*see table below*). Perhaps the slower Tmax observed with dermal administration (18-24 hrs in the minipig PK study) vs. oral administration (0.5-2 hrs) increases the threshold for dose-limiting cholinergic adverse effects.

<b>Comparison of SDZ ENA 713 and ZNS 114-666 Exposures after Oral vs. Dermal Administration of SDZ ENA 713 in Minipigs for Four Weeks</b>				
<b>Dose and Route</b>	<b>SDZ ENA 713 Cmax (ng/mL)</b>	<b>ZNS 114-666 Cmax (ng/mL)</b>	<b>SDZ ENA 713 AUC<sub>0-24 hr</sub> (ng*hr/mL)</b>	<b>ZNS 114-666 AUC<sub>0-24 hr</sub> (ng*hr/mL)</b>
6 mg/kg/day via Oral Gavage	27.8 (M)	392 (M)	69.2 (M)	1682 (M)
	14.4 (F)	457 (F)	24.4 (F)	1483 (F)
Six 18 mg/10 cm <sup>2</sup> patches/day	117 (M)	169 (M)	2033 (M)	2826 (M)
	137 (F)	155 (F)	2138 (F)	2471 (F)

(Reviewer's Table)

No new genetic toxicology studies were submitted.

No treatment-related findings were observed in a 98-99-week dermal carcinogenicity study in mice given rivastigmine in 100% ethanol at 0.25, 0.50, and 0.75 mg/kg/day, except for reduced body weight gain (16-17%) in high dose females. AUC<sub>0-24 hr</sub> exposures for rivastigmine in HD animals were only 28-44%, respectively, those observed in AD patients receiving Exelon® Patch 9.5 mg/24 hours. However, higher doses would probably not have been tolerated, since mice given rivastigmine dermally at 1.2 mg/kg/day in a previous study had to be sacrificed due to severe clinical signs after a single dose. The Executive Carcinogenicity Assessment Committee concluded that the study was adequate, that the doses were appropriate, and that the study was negative for carcinogenicity since there were no treatment-related tumor findings.

No new reproductive and developmental toxicology studies were submitted.

Evaluation of the potential for rivastigmine (or ENA713D) to induce local toxicity included nine primary skin irritation studies in rabbits, 11 contact hypersensitivity studies in guinea pigs, two primary eye irritation studies in rabbits, and one phototoxicity study in guinea pigs.

In eight primary irritation studies in rabbits, application of a single rivastigmine-containing patch (18 mg/10 cm<sup>2</sup>) onto the shaved dorsal skin of three animals per study for 4 hrs resulted in erythema (mostly very slight to well-defined) in 24/24 rabbits, and edema (mostly very slight) in 16/24 rabbits. Placebo patches evaluated in three of the eight studies induced either no irritation (one study) or irritation similar in frequency but slightly less severe than the corresponding drug-containing patch (2 studies). Four of these studies used ENA713D patch formulations that differed from the Final Market Image (FMI; i.e., the to-be-marketed formulation) in the amounts and/or types of adhesives and/or other excipients; however, the results with these various patch formulations did not differ from those using the FMI patches. In a separate study, a 4 cm<sup>2</sup> rivastigmine patch did not induce any irritation in rabbits after a 24-hr application. No systemic clinical signs were observed in any of the studies. The mean Primary Irritation Scores observed in most of the studies described above (based on the combined erythema and edema scores averaged over 24, 48, and 72 hrs post-application) did not exceed the established threshold for consideration as irritants to rabbit skin. However, the data support the conclusion that ENA713D has the potential to cause very slight to well-defined erythema and very slight edema after a single application.

Nine contact hypersensitivity studies were conducted in guinea pigs with ENA713D using the modified Buehler method. ENA713 patches (2.5, 4, 5, or 10 cm<sup>2</sup>) were applied to the shaved dorsal surface of guinea pigs for 6 hrs (2 studies) or 24 hrs (7 studies) once weekly during a 3-week induction period and during once during a challenge period two weeks following the last induction treatment. As in the primary irritation studies described above, four of these guinea pig studies were conducted using patches that differed from the FMI formulations in the amounts and/or types of adhesives and/or other excipients. Only one of the nine contact hypersensitivity studies demonstrated a sensitization response sufficient to be considered as a sensitizer. This positive outcome may be explained by the presence of an excipient \_\_\_\_\_ not present in any of the patches used in the other studies; however, definitive evidence for this would require further investigation.

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Most of these guinea pig studies showed slight to moderate erythema at the test site after the second and third induction treatments, but no skin changes after the challenge treatment. Placebo patches (included in four of these studies) also induced slight to moderate erythema during the induction phase. Spontaneous deaths of 1/20 to 8/20 animals were observed in all seven studies that used full-sized ENA713D patches (18 mg/10 cm<sup>2</sup>), necessitating reduction of dosing to quarter-sized patches (4.5 mg/2.5 cm<sup>2</sup>) for the third induction treatment and the challenge treatment in six studies. The deaths were attributed to cholinergic toxicity since occasional animals showed signs of tremor, dyspnea, ventral recumbency, and/or ruffled fur, and necropsies showed dilation and/or abnormal contents throughout the GI tract.

Two additional guinea pig contact hypersensitivity studies that involved intradermal injections of rivastigmine ( $\pm$  Freund's Complete Adjuvant) and dermal application of rivastigmine-impregnated filter paper in the induction and/or the challenge periods showed no positive skin reactions.

Two primary eye irritation studies in rabbits were performed with rivastigmine. In the first study, 0.1 mL pure liquid rivastigmine administered into the conjunctival sacs of three rabbits resulted in spontaneous death of all animals within one hour of dosing. In the second study, 10 uL rivastigmine administered into the cornea of the left eye resulted in clinical signs (slight to moderate tremor, impaired coordination, recumbency, and hyperreactivity to tactile stimulus) from one to five hours postdose. Eye reactions included miosis, moderate to marked lacrimation, loss of reactivity to light in the iris, and reddening and swelling of the conjunctivae starting ~1 hr postdose, and slight diffuse corneal opacities starting ~24 hrs postdose. All eyes were normal by 7 days postdose. The primary eye irritation score for SDZ ENA 713 at the dose of 10 uL was 3.44, which was classified as "not irritating" to the rabbit eye, according to commonly used criteria.

No phototoxicity was demonstrated in guinea pigs exposed to UV-A radiation for 90 minutes following a 30 minute dermal application of quarter-sized ENA713D patches. No dermal reaction was observed at the irradiated or non-irradiated sites of the animals treated with ENA713D or placebo patches. In positive control animals (treated with 8-methoxypsoralen), the irradiated site showed slight erythema, eschar formation, and exfoliation at 7 days postdose.

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In summary, the toxicology studies reviewed here have evaluated the potential for dermal rivastigmine to cause local or systemic toxicity, tumors, local irritation, sensitization, eye irritation, and phototoxicity. Repeated dermal dosing with rivastigmine in 50% ethanol in mice and rats showed dose-dependent cholinergic clinical signs, but no local toxicity. Repeated dosing with ENA713D in rabbits and minipigs did not cause systemic toxicity, but induced local irritation (edema in rabbits, and erythema in both species) that appeared to increase in incidence and severity with the number of patches applied and the frequency of re-application to the same skin site. A 98-99-week dermal study in mice given rivastigmine in 100% ethanol was negative for carcinogenicity. Primary rabbit irritation studies generally showed that single 4-hr applications of ENA713 mild skin irritation characterized by very slight to well-defined erythema and very slight edema. Contact hypersensitivity studies in guinea pigs generally showed mild irritation during the induction phase, but no evidence of a sensitization response. Direct application of rivastigmine to the cornea of rabbits resulted in included transient miosis, moderate to marked lacrimation, loss of reactivity to light in the iris, reddening and swelling of the conjunctivae, and transient slight diffuse corneal opacities at a dose that also caused tremor, impaired coordination, recumbency, and hyperreactivity to tactile stimulus. Finally, a 30-minute application of ENA713D did not cause phototoxicity in guinea pigs subsequently exposed to UV-A radiation for 90 minutes.

#### **2.6.6.10 Tables and Figures**

*(presented within individual studies)*

### **2.6.7 TOXICOLOGY TABULATED SUMMARY**

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## OVERALL CONCLUSIONS AND RECOMMENDATIONS

The key nonclinical pharmacokinetic/toxicokinetic studies supporting the current NDA for Exelon<sup>®</sup> Patch (rivastigmine transdermal system) included a minipig absorption/distribution/excretion study comparing IV, oral, and dermal administration of [<sup>14</sup>C]-rivastigmine and a metabolism study in a human skin model.

The minipig study demonstrated that administration of rivastigmine via dermal application of ENA713D essentially avoided the strong hepatic first-pass metabolism observed with low oral doses, resulting in much higher bioavailability of parent drug (12% for ENA713D at 18 mg/10 cm<sup>2</sup>, or ~2.3 mg/kg vs. 0.5% for oral at 1 mg/kg) and much lower metabolite to parent drug AUC ratios (ZNS 114-666:Rivastigmine = ~0.5 for dermal, 188 for oral).

These single dose PK results agreed with those obtained at steady-state from 4-week oral and dermal rivastigmine studies at 6-fold higher concentrations, as shown in the first two rows of the table below. AUC exposures were 29-fold (M) or 88-fold (F) higher after dermal compared to oral administration. ZNS 114-666: Rivastigmine AUC ratios were 24 (M) and 61 (F) after oral compared to 1.4 (M) and 1.2 (F) after dermal administration. It is remarkable that the much higher exposures to rivastigmine observed in the dermal 4-week minipig study did induce any systemic clinical signs while the high dose of 6 mg/kg/day in the oral 4-week minipig study appeared to be close to a maximum tolerated dose based on cholinergic toxicity: frequent, transient, slight to moderate tremors, slight lateral recumbency, and slight occasional decreased activity and salivation. The slower rise to peak levels with dermal administration may be responsible for this phenomenon.

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<b>Rivastigmine and ZNS 114-666<sup>1</sup> Exposures after Oral vs. Dermal Rivastigmine Administration in Minipigs and Humans</b>				
<b>Duration, Species and Dose</b>	<b>Rivastigmine C<sub>max</sub> (ng/mL)</b>	<b>ZNS 114-666<sup>1</sup> C<sub>max</sub> (ng/mL)</b>	<b>Rivastigmine AUC<sub>0-24 hr</sub> (ng*hr/mL)</b>	<b>ZNS 114-666<sup>1</sup> AUC<sub>0-24 hr</sub> (ng*hr/mL)</b>
4-Wk Minipig 6 mg/kg/day oral gavage	27.8 (M)	392 (M)	69.2 (M)	1682 (M)
	14.4 (F)	457 (F)	24.4 (F)	1483 (F)
4-Wk Minipig 12 patches/day (Exelon <sup>®</sup> Patch 9.5 mg/24 hours)	117 (M)	169 (M)	2033 (M)	2826 (M)
	137 (F)	155 (F)	2138 (F)	2471 (F)
26-Wk Minipig 2 patches/day (Exelon <sup>®</sup> Patch 9.5 mg/24 hours)	2.6 (M)	2.8 (M)	44 (M)	Not Calculated <sup>3</sup>
	3.2 (F)	2.7 (F)	52 (F)	
2-Week AD Patients <sup>2</sup> 1 patch/day (Exelon <sup>®</sup> Patch 9.5 mg/24 hours)	7.9	4.0	127	75.5
2-Week AD Patients <sup>2</sup> 6 mg bid oral capsule	29.3	12.5	191	142

*(Reviewer's Table: 1- ZNS 114-666 is also referred to as NAP226-90; 2-AD Patients were titrated up from lower doses of 1.5, 3, and 4.5 mg bid oral rivastigmine, or from Exelon<sup>®</sup> Patch 4.6 mg/24 hours, for two weeks each; 3-AUCs were not calculated because the concentration of ZNS 114-666 was below the limit of quantification at several time-points)*

The last two rows of the table above illustrate that the mean human C<sub>max</sub> and AUC exposures to rivastigmine and ZNS 114-666 at steady state following two weeks of treatment with the highest recommended clinical dermal dose (Exelon<sup>®</sup> Patch 9.5 mg/24 hour) are substantially lower than the corresponding exposures in humans after two weeks of treatment with the highest recommended clinical oral dose (6 mg bid Exelon<sup>®</sup> oral capsule); the ZNS 114-666:rivastigmine ratios are also similar. This helps to **ameliorate the sponsor's failure to explore a maximum tolerated or maximum feasible dose in the pivotal 26-week dermal minipig study**, which achieved exposures substantially lower than those in humans at the highest recommended clinical dermal dose (*compare rows 3 and 4 in the table above*). This reviewer estimates that the maximum feasible dose lies somewhere between four and nineteen 10 cm<sup>2</sup> patches per day (*see review of 26-week minipig study for details*). The lack of systemic toxicity in minipigs treated with twelve 10 cm<sup>2</sup> rivastigmine patches per day also provided important information that rivastigmine and ZNS 114-666 exposures  $\geq 15$ -fold higher than those at the highest recommended clinical dermal dose were tolerated for four weeks.

The in vitro metabolism study using cultured human foreskin fibroblasts provided somewhat limited, but important, evidence that metabolism of rivastigmine by the skin during dermal administration of ENA713D is not likely to result in the formation of new metabolites. The cells demonstrated very limited uptake of radiolabeled rivastigmine, and slowly produced only one metabolite, P71, the N-oxide of rivastigmine. Metabolite P71 was also produced in human liver slices in a separate study, but it was not present in the plasma of humans given a single oral dose of 1.0 or 2.5 mg [<sup>14</sup>C]-rivastigmine. It is difficult to know how closely the rivastigmine metabolism observed in this model system with human foreskin fibroblasts relates to that in the upper back skin of patients treated with Exelon<sup>®</sup> Patch. In vitro and/or ex vivo studies with dorsal skin from the minipig might help to clarify this issue.

The only metabolite evaluated in humans after dermal administration of rivastigmine was NAP226-90 (aka ZNS 114-666, the decarbamylated hydroxy derivative of rivastigmine), because this was the primary unconjugated metabolite observed in human plasma in a single dose oral study with 1.0 or 2.5 mg [<sup>14</sup>C]-rivastigmine tartrate. The most abundant metabolite present in this oral study, by far, was the sulfate conjugate of NAP226-90 (33.4% of plasma radioactivity 0.5 hr after the 2.5 mg dose), followed by unconjugated NAP226-90 (14.6%), followed by the sulfate conjugate of the N-demethylated derivative of rivastigmine (1.4%). Parent drug was not detected in plasma at these doses in this single dose study. Obviously, the metabolite profile at steady state after 6 mg bid oral rivastigmine was much different, since parent drug was present at higher levels than NAP226-90 (*see table above*). However, it seems likely that the primary plasma species present after both oral and dermal administration of rivastigmine in humans at the maximum recommended doses are parent drug, NAP226-90 (aka ZNS 114-666), and sulfated NAP226-90.

A milk transfer study conducted in rats given oral rivastigmine provided the data **supporting this reviewer's recommendation to include a statement in the "Nursing Mothers" section of the labeling to inform practitioners that concentrations of rivastigmine plus metabolites were approximately two times higher in milk than in plasma.**

Toxicology studies conducted in support of the current NDA for Exelon<sup>®</sup> Patch included repeated dose dermal studies in mice, rats, rabbits, and minipigs; a two-year dermal carcinogenicity study in mice; primary irritation studies in rabbits; contact hypersensitivity studies in guinea pigs; primary eye irritation studies in rabbits; and a phototoxicity study in guinea pigs.

Mice and rats treated dermally with rivastigmine in 50% ethanol once daily for up to 13 weeks (mice) or 4 weeks (rats) showed only clinical signs expected for a cholinergic drug: underactivity, piloerection, lacrimation, twitching, body tremors, irregular breathing, unusual posture, salivation, and/or yawning. No local toxicity was noted.

Repeated dosing in rabbits with ENA713D for up to four weeks was tolerated without any signs of systemic toxicity, but minor irritation characterized by erythema, edema, scaling, bruising, and/or scabbing occurred, and was attributed to the mechanical injury caused by successive application and removal of the strongly adhesive patch to and from the same skin site.

Repeated dose dermal studies in minipigs with ENA713D for up to 4 weeks demonstrated that moderate to severe irritation occasionally occurred in both drug-treated and placebo groups when patches were applied to the same site every day or every other day. Only minimal to slight erythema was generally observed when each skin site was re-used after six days. Drug-containing patches appeared to be slightly more irritating than placebo patches. No systemic toxicities were observed, even at rivastigmine exposures 4-10 fold higher than those in humans given oral Exelon at the maximum recommended dose. In contrast, oral rivastigmine induced typical cholinergic toxicity (tremors, salivation, and recumbency) in a 4-week minipig study at exposures lower than those in humans given oral Exelon at the maximum recommended dose. This large route-dependent difference in the exposure-response relationship remains unexplained.

In the pivotal 26-wk dermal minipig study, treatment with one or two 18 mg/10 cm<sup>2</sup> patches per day rotated such that each skin site was re-used every 12<sup>th</sup> day (or every 6<sup>th</sup> day in a second HD group) resulted in very slight to well-defined erythema at the application site from Wk 3 onward in drug-treated groups only. The frequency and severity of the erythema observed increased slightly with the application of 2 patches/day vs. 1 patch/day, and when sites were re-used every 6<sup>th</sup> day vs. every 12<sup>th</sup> day. However, no correlating histopathology changes were noted in the 26-wk study, and no other treatment-related changes were observed. Therefore, dosing in minipigs was not limited by systemic toxicity, but by the area of skin available for patch application. As explained above, this study did not include a maximum tolerated or maximum feasible dose.

The mean fraction of drug delivered from the patches over the 24-hr application period was 40-67% in minipig (average of all 4 repeat-dose studies), independent of dose or sex. The middle of this range, 53%, is identical to the percentage of drug delivered from the patch in clinical studies with Exelon<sup>®</sup> Patch 9.5 mg/24 hour (9.5 mg/18 mg = 53%).

No treatment-related findings were observed in a 98-99-week dermal carcinogenicity study in mice given rivastigmine in 100% ethanol at 0.25, 0.50, and 0.75 mg/kg/day, except for reduced body weight gain (16-17%) in high dose females. AUC<sub>0-24 hr</sub> exposures for rivastigmine in HD animals were only 28-44%, respectively, those observed in AD patients receiving Exelon<sup>®</sup> Patch 9.5 mg/24 hours. However, higher doses would probably not have been tolerated, since mice given rivastigmine dermally at 1.2 mg/kg/day in a previous study had to be sacrificed due to severe clinical signs after a single dose. The Executive Carcinogenicity Assessment Committee concluded that the study was adequate, that the doses were appropriate, and that the study was negative for carcinogenicity since there were no treatment-related tumor findings.

Rat primary irritation studies generally showed that 4-hr application of ENA713D induced very slight to well-defined erythema and very slight edema. Contact hypersensitivity studies in guinea pigs generally showed that ENA713D did not cause sensitization; however, mild irritation was observed at the test site during the induction phase. Additionally, dose-related spontaneous deaths observed after the second or third induction treatment only in animals treated with full-sized 10 cm<sup>2</sup> patches, were attributed to cholinergic toxicity.

Rivastigmine applied directly to the eye caused miosis, moderate to marked lacrimation, loss of reactivity to light in the iris, reddening and swelling of the conjunctivae, and transient corneal opacities, but the eyes returned to normal by seven days after dosing.

ENA713D was found to be non-phototoxic in guinea pigs treated for 30 minutes followed by UV-A irradiation for 90 minutes. Rivastigmine base absorbs UV radiation maximally at ~210-225 nm, though a smaller peak occurs at ~270 nm; no absorption was observed within the UV-A range of 320-400 nm.

The drug product does not contain any novel excipients. However, this reviewer expressed some concern over the specifications of one particular excipient. \_\_\_\_\_

\_\_\_\_\_ component of the drug product matrix.

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*Conclusions:*

It is unfortunate that the minipig study comparing oral and dermal with [<sup>14</sup>C]-rivastigmine did not include evaluation of metabolites other than ZNS 114-666 and that a comprehensive metabolism study was not conducted in humans at the maximum recommended clinical doses. However, the similarity of the ZNS 114-666:rivastigmine ratios in humans at steady state following treatment at the maximum recommended oral and dermal doses, and the substantially lower exposures after dermal vs. oral administration at these doses, provide reasonable assurance that dermal administration of rivastigmine in humans is not likely to result in important changes in the plasma metabolite profile

The pivotal 26-week dermal minipig study did not evaluate a maximum tolerated or maximum feasible dose of rivastigmine. At the highest dose tested, two 10 cm<sup>2</sup> patches per day, no systemic toxicity and only mild skin irritation was observed. However, the similarity between the rivastigmine and ZNS 114-666 exposures in humans after oral and dermal administration noted above, combined with the lack of systemic toxicity noted in minipigs treated with twelve 10 cm<sup>2</sup> rivastigmine patches per day for four weeks despite exposures  $\geq$  15-fold higher than those at the highest recommended clinical dermal dose, provide a compelling argument that no new toxicities are likely to emerge from a chronic toxicity study in minipigs at a maximum tolerated or maximum feasible dose.

The studies submitted demonstrate that administration of Exelon<sup>®</sup> Patch is likely to cause mild local skin irritation that could progress to severe irritation if the same skin sites are used more often than once every sixth day. The evidence also suggests that systemic toxicity may be lower with dermal administration than with oral administration at comparable exposures.

*Unresolved toxicology issues:* None.

*Recommendations:*

From a Pharmacology/Toxicology perspective, this NDA is adequate to be approved, provided appropriate changes are made to the proposed labeling.

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**Suggested labeling:**

**Sponsor's proposed labeling:**

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*Reviewer's Comments:*

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*Reviewer's Recommended Revisions to the Sponsor's Suggested Labeling:*

**8.1 Pregnancy**

**Pregnancy Category B:** There are no adequate or well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, the Exelon Patch should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. No dermal reproduction studies in animals have been conducted. Oral reproduction studies conducted in pregnant rats at doses up to 2.3 mg-base/kg/day and in pregnant rabbits at doses up to 2.3 mg-base/kg/day revealed no evidence of teratogenicity. Studies in rats showed slightly decreased fetal/pup weights, usually at doses causing some maternal toxicity.

**8.3 Nursing Mothers**

Milk transfer studies in animals have not been conducted with dermal rivastigmine. In rats given rivastigmine orally, concentrations of rivastigmine plus metabolites were approximately two times higher in milk than in plasma. It is not known whether rivastigmine is excreted in human breast milk. Exelon Patch (rivastigmine transdermal system) has no indication for use in nursing mothers.

Sponsor's proposed labeling:

## 12. CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

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### 12.2 Pharmacodynamics

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Current labeling for Exelon capsules and oral solution:

#### CLINICAL PHARMACOLOGY

##### Mechanism of Action

Pathological changes in Dementia of the Alzheimer type and Dementia associated with Parkinson's disease involve cholinergic neuronal pathways that project from the basal forebrain to the cerebral cortex and hippocampus. These pathways are thought to be intricately involved in memory, attention, learning, and other cognitive processes. While the precise mechanism of rivastigmine's action is unknown, it is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by cholinesterase. If this proposed mechanism is correct, Exelon's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that rivastigmine alters the course of the underlying dementing process. After a 6-mg dose of rivastigmine, anticholinesterase activity is present in CSF for about 10 hours, with a maximum inhibition of about 60% 5 hours after dosing.

In vitro and in vivo studies demonstrate that the inhibition of cholinesterase by rivastigmine is not affected by the concomitant administration of memantine, an N-methyl-D-aspartate receptor antagonist.

*Reviewer's Comments:*

Since this submission did not include any pharmacology studies supporting the proposed changes in the description of the mechanism of action and pharmacodynamics of rivastigmine, most of the wording in the Mechanism of Action section of the approved label should be retained with slight modifications in the 12.1 Mechanism of Action section of the new label, except for two statements that should be moved to the new 12.2 Pharmacodynamics section.

*Reviewer's Recommended Revisions to the Sponsor's Suggested Labeling:***12. CLINICAL PHARMACOLOGY****12.1 Mechanism of Action**

Pathological changes in Dementia of the Alzheimer's type and Dementia associated with Parkinson's disease involve cholinergic neuronal pathways that project from the basal forebrain to the cerebral cortex and hippocampus. These pathways are thought to be intricately involved in memory, attention, learning, and other cognitive processes. While the precise mechanism of rivastigmine's action is unknown, it is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis by cholinesterase. If this proposed mechanism is correct, rivastigmine's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that rivastigmine alters the course of the underlying dementing process.

**12.2 Pharmacodynamics**

After a 6-mg oral dose of rivastigmine in humans, anticholinesterase activity is present in CSF for about 10 hours, with a maximum inhibition of about 60% 5 hours after dosing.

*In-vitro* and *in-vivo* studies demonstrate that the inhibition of cholinesterase by rivastigmine is not affected by the concomitant administration of memantine, an N-methyl-D-aspartate receptor antagonist.

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Sponsor's proposed labeling:

**13. NONCLINICAL TOXICOLOGY**

**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

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Current labeling for Exelon capsules and oral solution:

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

In carcinogenicity studies conducted at dose levels up to 1.1 mg-base/kg/day in rats and 1.6 mg-base/kg/day in mice, rivastigmine was not carcinogenic. These dose levels are approximately 0.9 times and 0.7 times the maximum recommended human daily dose of 12 mg/day on a mg/m<sup>2</sup> basis.

Rivastigmine was clastogenic in two in vitro assays in the presence, but not the absence, of metabolic activation. It caused structural chromosomal aberrations in V79 Chinese hamster lung cells and both structural and numerical (polyploidy) chromosomal aberrations in human peripheral blood lymphocytes. Rivastigmine was not genotoxic in three in vitro assays: the Ames test, the unscheduled DNA synthesis (UDS) test in rat hepatocytes (a test for induction of DNA repair synthesis), and the HGPRT test in V79 Chinese hamster cells. Rivastigmine was not clastogenic in the in vivo mouse micronucleus test.

Rivastigmine had no effect on fertility or reproductive performance in the rat at dose levels up to 1.1 mg-base/kg/day. This dose is approximately 0.9 times the maximum recommended human daily dose of 12 mg/day on a mg/m<sup>2</sup> basis.

*Reviewer's Comments:*

The \_\_\_\_\_ sections should be removed entirely, since they do not impart clinically significant data necessary for safe and effective use of the drug in humans. \_\_\_\_\_

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The Mutagenicity paragraph should remain unchanged from the wording in the genotoxicity paragraph of the approved label for oral Exelon, since no new genotoxicity data have been submitted.

The Carcinogenicity paragraphs should be moved ahead of the Mutagenesis section, and should include the description of the oral mouse and rat studies from the approved label for Exelon (revised to eliminate dose comparisons to the dermal product) and a similar description of the new dermal carcinogenicity study in mice, including exposure comparisons based on AUC.

The Reproductive Toxicity paragraph should be limited to the wording in the corresponding paragraph of the approved label for oral Exelon, revised to eliminate dose comparisons to the dermal product. A statement should be added to clarify that no dermal reproduction studies have been conducted. Other reproductive toxicity results are more appropriately included in the Pregnancy section, rather than here in the Impairment of Fertility section.

Section 13.2 should be deleted, since the potential for dermal irritation is adequately presented in the "ADVERSE REACTIONS" section and the "Method of Administration" section. The inclusion of negative results from the guinea pig phototoxicity study would not improve human safety.

*Reviewer's Recommended Revisions to the Sponsor's Suggested Labeling:*

### 13 NONCLINICAL TOXICOLOGY

#### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In oral carcinogenicity studies conducted at doses up to 1.1 mg-base/kg/day in rats and 1.6 mg-base/kg/day in mice, rivastigmine was not carcinogenic.

In a dermal carcinogenicity study conducted at doses up to 0.75 mg-base/kg/day in mice, rivastigmine was not carcinogenic. The mean rivastigmine plasma exposure (AUC) at this dose was 0.3-0.4 times that observed in Alzheimer's disease patients at the recommended clinical dose (one Exelon Patch 9.5 mg/24 hours).

Rivastigmine was clastogenic in two in vitro assays in the presence, but not the absence, of metabolic activation. It caused structural chromosomal aberrations in V79 Chinese hamster lung cells and both structural and numerical (polyploidy) chromosomal aberrations in human peripheral blood lymphocytes. Rivastigmine was not genotoxic in three in vitro assays: the Ames test, the unscheduled DNA synthesis (UDS) test in rat hepatocytes (a test for induction of DNA repair synthesis), and the HGPRT test in V79 Chinese hamster cells. Rivastigmine was not clastogenic in the in vivo mouse micronucleus test.

No fertility or reproduction studies have been conducted in animals treated with dermal rivastigmine. Rivastigmine had no effect on fertility or reproductive performance in rats at oral doses up to 1.1 mg-base/kg/day.

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/s/  
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David Hawver  
7/6/2007 06:28:20 PM  
PHARMACOLOGIST

Lois Freed  
7/6/2007 06:31:37 PM  
PHARMACOLOGIST  
Please see memo for comments.

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