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**Briefing Document for NDA 20-644
Psychopharmacologic Drugs Advisory Committee
(PDAC) Meeting**

ERRATUM

Product: Serdolect[®]

Generic name: Sertindole
Sponsor: H. Lundbeck A/S
2500 Valby (Copenhagen), Denmark
Date: 27 March 2009

Inaccuracies have been identified in the Briefing Materials (dated 9 March 2009) for the FDA Advisory Committee for NDA 20-644 (sertindole). These inaccuracies are corrected in this erratum.

None of the corrections has an impact on the overall interpretation of the data.

Section 2.3.5.1 Demographic Characteristics – The Main SCoP Study

Page 42, Panel 16

The numbers for the rows *Primary reason for prescription of study drug* and *Primary reason for stopping study drug* were switched for sertindole and risperidone (shaded table cells); this has been corrected in the panel below.

Panel 16 The SCoP Study – Patient Characteristics

	Sertindole	Risperidone
Patients treated	4905	4904
[Europe / Asia]	[3545 / 1360]	[3543 / 1361]
Sex (% male)	55	55
Mean age (years)	38.4	38.3
[range]	[18 - 84]	[18 - 81]
Age groups (%)	44 / 54 / 2	44 / 54 / 2
<35 / 35-65 / ≥65		
Duration of schizophrenia (%)	30 / 26 / 42	30 / 26 / 42
<5 years / 5-10 years / >10 years		
Last antipsychotic treatment before study inclusion (%)		
Typical/ atypical/ both	53 / 36 / 10	53 / 37 / 10
Monotherapy/ polytherapy	77 / 23	77 / 23
Primary reason for prescription of study drug (%)		
Lack of efficacy	51.8	52.6
Adverse drug reaction	22.8	21.8
Patient's choice	20.2	19.9
Non or poor compliance	3.2	3.4
Other	1.8	2.1
Primary reason for stopping study drug (%)		
Lack of efficacy	7.9	7.7
Serious adverse event	2.0	1.3
Non-serious adverse event	8.0	3.7
Non-compliance	6.2	5.3
Patient / relative decision	22.3	18.7
Investigator decision	1.2	1.7
Pregnancy	<1	<1
Other	1.9	2.1
Not given	14.1	12.3
Sponsor study closure	36.0	47.0

Section 4.4.3 Characteristics of Suicide Attempts

Page 68, Panel 36

Two numbers have been corrected and one has been added (shaded table cells); all three are marked in bold in the panel below.

Panel 36 The SCoP Study – Characteristics of Suicide Attempts (C-CASA ORT+1 day Period)

Type of Suicide Attempt	Sertindole n (%)	Risperidone n (%)
Total	36	54
Non-violent	23 (64)	25 (46)
Overdose	20	21
Poisoning	3	4
Violent	13 (36)	28 (52)
Cutting	1	6
Drowning	0	1
Hanging	6	12
Jumping	6	9
Unknown	0	1 (2)

Section 4.4.4.1 C-CASA of Suicide Events

Page 70, above Panel 38 and Panel 38

The following text has been added:

Two suicide attempts were not included in the original C-CASA analysis: one was a simple omission (it was included in the MedDRA analyses and in the clinical study report) and the other was identified after the SCoP study had been reported. Both attempts occurred during the ORT+1, one in the sertindole group (during the first year of treatment) and the other in the risperidone group (after 1 year of treatment). The two cases were classified by experts at Columbia University according to C-CASA as suicide attempts. A sensitivity analysis including these 2 suicide attempts is included in Panel 38 and the results are very similar to those in the original C-CASA analysis.

The results of the sensitivity analysis are included in the panel below (shaded table cells).

Panel 38 The SCoP Study – Suicide and Suicide Attempt Rates as Classified According to C-CASA (ORT+1 day Period)

Events	Sertindole Number of Suicide Attempts (Rate per 100 PYE)	Risperidone Number of Suicide Attempts (Rate per 100 PYE)	Hazard Ratio ^a	Two-sided p-value
All patients treated (n)	4905	4904		
Suicide attempts (fatal plus non-fatal)	36 (0.57)	54 (0.75)	0.661	0.0594
Suicide attempts (fatal plus non-fatal) 1-year	27 (0.81)	47 (1.28)	0.546	0.0147
Completed suicides	9 (0.14)	19 (0.26)	0.502	0.0890
High-risk patients ^b (n)	348	335		
Suicide attempts (fatal plus non-fatal)	14 (3.25)	21 (5.15)	0.585	0.1218
Suicide attempts (fatal plus non-fatal) 1-year	13 (5.65)	20 (9.22)	0.567	0.1126
Sensitivity analysis				
All patients treated (n)	4905	4904		
Suicide attempts (fatal plus non-fatal)	37 (0.58)	55 (0.76)	0.669	0.0630
Suicide attempts (fatal plus non-fatal) 1-year	28 (0.84)	47 (1.28)	0.567	0.0206

PYE: patient years of exposure

a Cox's Proportional Hazards Model

b Patients who had a previous suicide attempt within the last 5 years before entering the study.

Section 5.7.2 Weight, BMI, and Waist Circumference

Page 86, Panel 55

Two numbers have been corrected (shaded table cells) and are marked in bold in the panel below.

Panel 55 SCoP Metabolic Sub-study – Mean Changes from Baseline in Weight, BMI, and Waist Circumference (ORT Period)

Variable	Time Point	Sertindole	Sertindole	Risperidone	Risperidone
		N	Mean (±SD)	N	Mean (±SD)
Weight (kg)	Baseline	107	71.7 (±13.1)	116	73.4 (±13.8)
	ΔWeek 12	92	1.3 (±3.1)	108	1.1 (±2.6)
	ΔWeek 24	78	1.6 (±3.7)	97	1.4 (±3.1)
	ΔWeek 36	54	2.2 (±4.0)	63	2.0 (±3.7)
	ΔLast Assessment	107	1.8 (±3.5)	116	1.7 (±3.4)
BMI (kg/m ²)	Baseline	107	24.7 (±3.8)	116	25.6 (±4.5)
	ΔWeek 12	92	0.5 (± 1.0)	108	0.4 (±0.9)
	ΔWeek 24	78	0.6 (±1.3)	97	0.5 (±1.1)
	ΔWeek 36	54	0.7 (±1.4)	63	0.7 (±1.3)
	ΔLast Assessment	107	0.6 (±1.2)	116	0.6 (±1.2)
Waist Circumference (cm)	Baseline	107	84.8 (±13.2)	116	85.8 (±13.8)
	ΔWeek 12	93	1.1 (±4.1)	108	1.1 (±3.6)
	ΔWeek 24	78	1.0 (±5.1)	97	1.6 (±3.8)
	ΔWeek 36	54	1.5 (±6.0)	63	2.0 (±3.9)
	ΔLast Assessment	107	1.4 (±4.8)	116	1.6 (±3.9)

SD: standard deviation

Section 5.7.3 Fasting Serum Lipids

Page 88, Panel 57

One number has been corrected (shaded table cell) and is marked in bold in the panel below.

Panel 57 SCoP Metabolic Sub-study – Mean Changes from Baseline in Fasting Serum Lipids (ORT Period)

Variable	Time Point	Sertindole		Risperidone	
		N	Mean (±SD)	N	Mean (±SD)
Triglycerides (mmol/L)	Baseline	89	1.25 (±0.5)	103	1.52 (±1.0)
	ΔWeek 12	71	0.00 (±0.7)	93	-0.15 (±0.9)
	ΔWeek 36	33	-0.05 (±0.6)	47	-0.04 (±0.9)
	ΔLast Assessment	89	0.03 (±0.6)	103	-0.04 (±0.7)
Total cholesterol (mmol/L)	Baseline	89	4.8 (±1.2)	103	5.0 (±1.3)
	ΔWeek 12	71	0.11 (±1.2)	93	-0.12 (±1.1)
	ΔWeek 36	33	0.13 (±1.3)	47	-0.06 (±1.3)
	ΔLast Assessment	89	0.05 (±1.2)	103	-0.09 (±1.2)
HDL-cholesterol (mmol/L)	Baseline	89	1.29 (±0.4)	103	1.26 (±0.3)
	ΔWeek 12	71	0.10 (±0.4)	93	0.01 (±0.3)
	ΔWeek 36	33	0.12 (±0.4)	47	0.0 (±0.4)
	ΔLast Assessment	89	0.06 (±0.4)	103	0.02 (±0.3)
LDL-cholesterol (mmol/L)	Baseline	89	3.0 (±1.0)	100	3.1 (±1.1)
	ΔWeek 12	71	0.00 (±1.0)	89	-0.08 (±0.9)
	ΔWeek 36	33	0.03 (±1.1)	44	-0.02 (±1.2)
	ΔLast Assessment	89	-0.03 (±1.0)	100	-0.10 (±1.0)

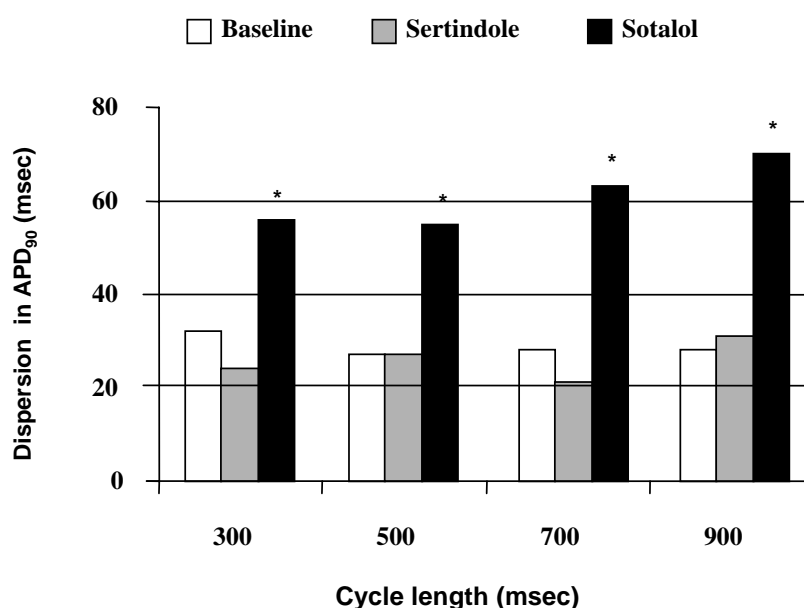
SD: standard deviation

Section 5.8.2.4 Transmural Dispersion

Page 95, Panel 64

The order of the cycle lengths (x-axis) was reversed and the indications of statistical significances were missing. This has been corrected in the panel below.

Panel 64 Effect of Sertindole and dl-sotalol on Transmural Dispersion in an Isolated Perfused Rabbit Heart



* p < 0.05

Recordings of transmural dispersion over a range of different cardiac rates in AV-node ablated perfused rabbit hearts. Dispersion is measured by the difference in action potential recordings (APD₉₀) between endocardial and epicardial electrodes. White bars indicate baseline recordings, grey bars 1 μ M of sertindole and black bars 10 μ M of the positive control, dl-sotalol. Only dl-sotalol causes an increase in transmural dispersion compared to baseline. Cycle lengths of 300, 500, 700, and 900 msec represent hearts rates of 200, 120, 85 and 67 beats per minute.

Section 5.8.3.2 QT Interval Results

Pages 98 and 99, Panel 68

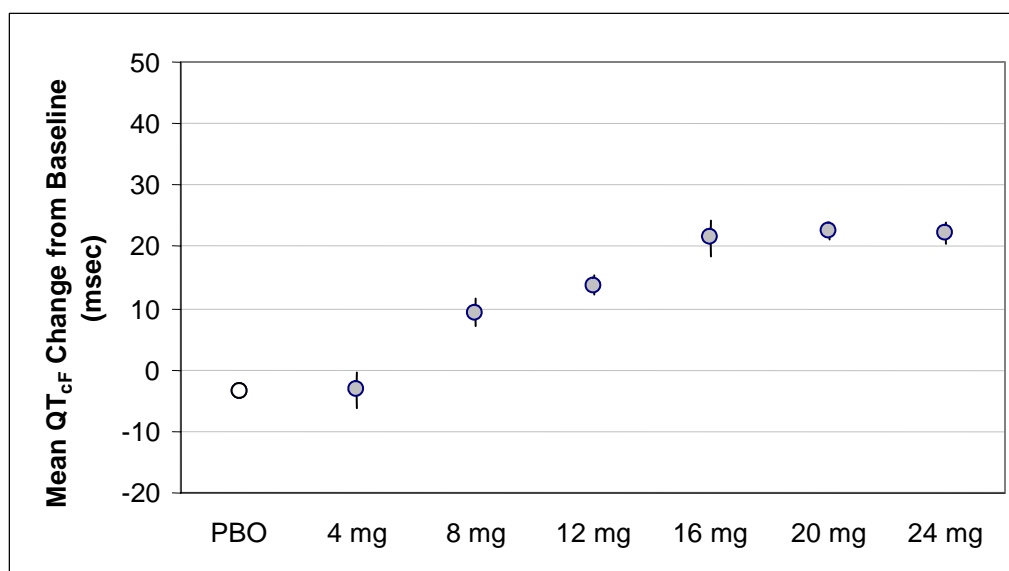
For consistency with the other QT_c data presented, Panel 68 has been replaced to show the mean change in QT_{cF} instead of the mean change in QT_{cB}.

The text below Panel 67 has been updated accordingly:

From the original reading of the ECGs, it was demonstrated that the QT/QT_c interval change from baseline is dose dependent.

In agreement with the nonclinical data, the mean QT_c interval prolongation appears to level off, with increasing concentration/dose, as seen for the dosages between 16 and 24mg/day (Panel 68).

Panel 68 Short-term Fixed-dose Studies – Mean Change in the QT_{cF} Interval by Dose (Original Overread)



Data source: patients with a baseline and at least one post-treatment QT_c value in Studies M92-762, M92-817, M93-098, M93-113, and M95-342. N=1296.

Section 5.11 Overdoses

Page 116, Panel 85

The ECG description has been revised for Case 0970115. The revision is marked in bold in the panel below.

Panel 85 Global Safety Database – The 5 Cases With the Highest Overdose of Sertindole

Case ID (Source)	Age/ Sex	Sertindole dose	QT _c	Narrative
Non-fatal				
1027877 (The SCoP study)	28/F	2560mg	-	Overdose of 2560mg sertindole and an unknown quantity of insecticide in an attempted suicide. The patient vomited and was hospitalised and further treated with gastric lavage. No associated symptoms reported. The patient recovered and was discharged the next day.
0950493 (Clinical studies)	26/M	840mg	-	Overdose of 840mg sertindole and 37.5mg lorazepam in an attempted suicide. The patient was hospitalised and made a full recovery. No associated symptoms or treatment were reported.
0970115 (Clinical studies)	34/M	720mg	520msec	Mixed overdose of sertindole (720mg) and lorazepam (30mg) in a suicide attempt. ECG showed AV-block, QT prolongation and TdP . The patient recovered without intervention.
0970292 (Spontaneous report)	34/M	672mg	509msec	Overdose of 672mg sertindole, 120mg citalopram, and 1L alcohol in an attempted suicide. The patient was hospitalised with the following symptoms: dyspnoea, somnolence, and chest pain. ECG recording showed QT _c at 509msec. The patient made a full recovery.
Fatal				
0960013 (Clinical studies)	22/M	660mg	-	Overdose of 660mg sertindole, 125mg lorazepam, and alcohol. The patient was hospitalised the next day but did not present any symptoms. The patient died 6 hours after admission. Post mortem blood samples showed sertindole concentration 8-10 times that expected at 24mg daily dose. No other information was provided.