DOXEPIN 10 MG, 25 MG & 50 MG CAPSULES

2.5 Clinical Overview

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MODULE 2 OVERALL SUMMARIES

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Contents

Abbreviations

5-HT	5-hydroxytryptamine (serotonin)
AE	adverse event
API	active pharmaceutical ingredient
AUC	area under the curve
BPRS	Brief Psychiatric Rating Scale
CGI	Clinical Global Impression
CI	confidence interval
CKD	chronic kidney disease
C_{max}	maximum plasma concentrations
CNS	central nervous system
CRD	Centre for Reviews and Dissemination
DMD	desmethyldoxepin
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DV	distribution volume
ECG	electrocardiogarm
EEG	electroencephalogram
EU	European Union
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
H_1	histamine-1 receptor
HAMA	Hamilton Psychiatric Rating Scales for Anxiety
HAMD	Hamilton Psychiatric Rating Scales for Depression
HPLC	high-performance liquid chromatography
IBS	irritable bowel syndrome
IM	intramuscular(ly)
IP	intraperitoneal(ly)
IV	intravenous(ly)
K_i	inhibitory constant
M	muscarinic
MADRS	Montgomery-Asberg Depression Rating Scale
MAP	mean arterial blood pressure
MDD	major depressive disorder
NE	norepinephrine
PET	positron emission tomography
PGI	Patient Global Impression

PO	per os (oral)
RBC	red blood cell
REM	rapid eye movement
SAE	serious adverse event
SD	standard deviation
SDS	Self-Rating Depression Scale
SEM	standard error of mean
SmPC	Summary of Product Characteristics
SNS	sympathetic nervous system
sTST	subjective total sleep time
sWASO	subjective wake after sleep onset
SWS	slow wave sleep
UK	United Kingdom
US	United States
WASO	wake time after sleep onset
WITT	Witten born Psychiatric Rating Scale

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2.5.1 Product Development Rationale

Doxepin 10 mg, 25 mg and 50 mg Capsules of Morningside Healthcare Ltd, United Kingdom (UK) are indicated for the treatment of symptoms of depressive illness, especially where sedation is required. Each type of capsules contains the indicated amount of doxepin hydrochloride.

Doxepin hydrochloride is a dibenzoxepin derivative designated chemically as (E/Z)-3-(dibenzo[b,e]oxepin-11(6H)-ylidene)-N,N-dimethylpropan-1-amine hydrochloride (Fig. 1).

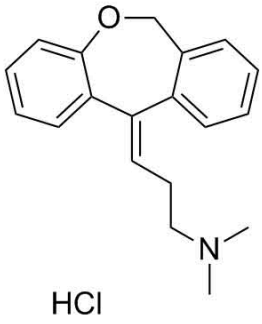

Figure 1 Structural formula of doxepin hydrochloride.

Doxepin is a psychotropic agent with tricyclic antidepressant and anxiolytic properties, and with antipruritic and sedative activities. Doxepin blocks the reuptake of norepinephrine (NE) and serotonin [5-hydroxytryptamine (5-HT)] into presynaptic terminals thereby prolonging the availability of monoaminergic neurotransmitters within the synaptic cleft and enhancing their action leading to sedative effects ([redacted]). Doxepin has antagonistic effects on histamine-1 receptor (H_1) ([redacted]), 5-HT_2 ([redacted]), α_1-adrenergic ([redacted]), and muscarinic (M) receptors ([redacted]). The antipruritic effect of this agent is the result of inhibiting histamine receptors. Doxepin is a tertiary amine that can be presented as an (E) and (Z) stereoisomer from which the (Z) form corresponds to cidoxepin. Doxepin is marketed as a mixture of geometric isomers such that the more active Z-isomer comprises only 15% of the total doxepin whereas the less active E-isomer makes up the remaining 85%. Doxepin is closely related in structure to tricyclic antidepressants and shares many properties with some of the members of this family such as amitriptyline, clomipramine, desipramine, imipramine, nortriptyline, protriptyline and trimipramine.

Depressive disorders are characterized by sadness severe or persistent enough to interfere with function and often by decreased interest or pleasure in activities ([redacted]). The exact cause is unknown but probably involves heredity, changes in neurotransmitter levels, altered neuroendocrine function, and psychosocial factors ([redacted]; [redacted]). Diagnosis is based on history ([redacted]). The term depression is often used to refer to any of several depressive disorders. Some are classified in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) by specific symptoms ([redacted]) such as

a) Major depressive disorder (often called major depression)
b) Persistent depressive disorder (dysthymia)
c) Other specified or unspecified depressive disorder.

Others are classified by aetiology such as

a) Premenstrual dysphoric disorder
b) Depressive disorder due to another medical condition
c) Substance/medication-induced depressive disorder.

Depression is associated with abnormalities in sleep pattern that include disturbances of sleep continuity, diminished slow-wave sleep (SWS) and altered rapid eye movement (REM) sleep parameters. Although none of the reported changes in sleep are specific to depression, many of them, e.g., increased REM density and reduced amount of SWS in the first sleep cycle, are used as biological markers for research on depression and in the development of antidepressant drugs ([redacted]). Depressive disorders occur at any age but typically develop during the mid-teens, 20s, or 30s ([redacted]). In primary care settings, as many as 30% of patients report depressive symptoms, but less than 10% have major depression ([redacted]).

Doxepin was discovered in Germany in 1963 and was introduced in the United States (US) as an antidepressant in 1969 ([redacted]). In 2010, it was approved at very low doses for the treatment of insomnia in the US ([redacted]). Doxepin is one of the most frequently prescribed antidepressants ([redacted]).

The excipients in Doxepin 10 mg, 25 mg and 50 mg Capsules of Morningside Healthcare Ltd, UK are approved and established agents in widespread use in the pharmaceutical manufacturing industry.

The Applicant, Morningside Healthcare Ltd., UK, is preparing an Article 10(1) generic application for Doxepin 25 mg and 50 mg Capsules and an Article 10(3) hybrid application for Doxepin 10 mg Capsule demonstrating the medicinal product, its active

substance, pharmaceutical form, strengths, therapeutic indications, route of administration in comparison to the reference medicinal product, as well as details related to the bio-equivalence in accordance with European Union (EU) Directive 2001/83/EC.

This clinical overview of doxepin takes into account that one of the medicinal products the Marketing Authorization will be applied for, Doxepin 50 mg Capsule of Morningside Healthcare Ltd, UK is essentially similar to an original medicinal product, Doxepin Hydrochloride BP 50 mg capsules of Marlborough Pharmaceuticals Ltd., UK).

Doxepin, the active substance, is of well-established use, recognised as safe and effective, has high therapeutic margin and no particular concern in terms of toxicity. The excipients in Doxepin 10 mg, 25 mg and 50 mg of Morningside Healthcare Ltd, UK are approved and established agents in widespread use in the pharmaceutical manufacturing industry.

This clinical overview has been prepared upon a systematic search through [redacted] to identify peer-reviewed articles evaluating the relevant clinical pharmacodynamic, pharmacokinetic and safety/tolerability aspects of using doxepin as active pharmaceutical ingredient (API) in Doxepin 10 mg, 25 mg and 50 mg Capsules of Morningside Healthcare Ltd, UK.. This systematic search using the keywords 'doxepin' yielded altogether [redacted] publications that were narrowed by keywords such as '[redacted]', '[redacted]', '[redacted]', '[redacted]', '[redacted]', '[redacted]', '[redacted]', '[redacted]', '[redacted]', '[redacted]', '[redacted]', '[redacted]', '[redacted]', '[redacted]'. [redacted] was used for permitting [redacted] of the used terms.

This Clinical Overview has been prepared as part of marketing authorisation application to market a formulation of Doxepin 10 mg, 25 mg and 50 mg Capsules. All pharmacokinetic, efficacy and safety data described in this Clinical Overview is based on information retrieved from publicly available literature.

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2.5.2 Overview of Biopharmaceutics

2.5.2.1 Overview of Reference Formulation and Similarity

An open-label, balanced, randomized, single-dose, two-treatment, two-sequence, two-period, crossover bioequivalence study of Doxepin 50 mg capsules (Test: Morningside Healthcare Ltd., UK) and Doxepin Hydrochloride BP 50 mg capsules (Reference: Marlborough Pharmaceuticals Ltd., 35A High Street, Marlborough, SN8 1LW, UK) was performed in 40 healthy, adult, male subjects under fasting conditions to compare the rate and extent of absorption of Test and Reference products (*Clinical Study Report,* [redacted]).

Healthy, non-smoking, willing male volunteers aged between 18 and 45 years (inclusive) were selected on the basis of laboratory evaluations during screening, demography (age, height, weight and BMI), questioning on medical history, clinical examination along with vital signs, chest X-ray (P/A view) and electrocardiogarm (ECG) recordings. A urine screen for drugs of abuse and an alcohol breath test were undertaken at the time of check-in of each period. All study related procedures, duration, dates and timings, information on the study treatments and confidentiality of the subjects' data were explained clearly to the subjects by clinical personnel during the informed consent procedure. Subjects who signed the consent form and showed their willingness to participate in the study were enrolled. Subjects who were eligible when assessed against the inclusion and exclusion criteria and who were found to be healthy on physical examination with laboratory investigation values within reference limits were considered for admission into the study. Subjects whose pre-study laboratory values were outside the reference range were also considered for participation provided these values were considered clinically non-significant by the investigators. The eligible subjects reported to the study site on 17th Aug 19 for period 01 and on 31st Aug 19 for period 02. Treatments were allocated to subjects as per the randomization schedule generated using statistical techniques with SAS® (SAS Institute Inc., USA) version 9.4. Blood samples were drawn before dosing (0.00 hour) and up to 72.00 hours after dosing in each period. The administration of each product was followed by a washout period of 14 days. Plasma concentrations of Doxepin were assayed using a validated LC-MS/ MS method at [redacted]

After an overnight fast of at least 10.00 hours, a single dose of either the Test or the Reference product was administered orally to each subject while in a sitting position with approximately 240 mL of water followed by a thorough mouth check to ensure

that the drug has been swallowed. The subject was instructed not to chew or crush the capsule but to swallow it whole. The total duration of the study was 19 days from the day of check-in of the first period till the check-out of Period 02.

The decision as to whether or not the test product is bioequivalent to the reference product after single-dose administration under fasting conditions was taken based on 90% confidence intervals of the differences of least squares means of ln-transformed maximum plasma concentrations (C_{max}) and area under the curve $(AUC)_{0-72h}$ of doxepin. The acceptance range for bioequivalence is that the entire confidence intervals for the difference of means of ln-transformed C_{max} and AUC_{0-72h} should fall within 80.00 – 125.00%. Employing the estimated concentration-time profiles of doxepin, the following pharmacokinetic parameters were calculated by using the non-compartmental model of Phoenix WinNonlin, version 8.0 (Phoenix 1.3):

- Primary pharmacokinetic parameters: C_{max} and AUC_{0-72h}
- Secondary pharmacokinetic parameters: T_{max}, $t_{1/2}$, and K_{el}.

Statistical analysis of the pharmacokinetic parameters was carried out using the PROC GLM procedure of SAS® (SAS Institute Inc., USA) version 9.4. Descriptive statistics were computed and reported for the pharmacokinetic parameters. The ln-transformed pharmacokinetic parameters C_{max} and AUC_{0-72h} were subjected to Analysis of Variance (ANOVA) for bioequivalence assessment. The model included sequence, subject (sequence), period and formulation effects as fixed effects factors.

Safety Assessment

All subjects who had received at least one dose of investigational product were included in the safety evaluation. Safety assessment was based on clinical laboratory evaluation, chest X-ray (P/A view), ECG recordings, Clinical examination along with vital signs (axillary temperature, radial pulse rate, sitting blood pressure, lying blood pressure, standing blood pressure and respiratory rate) well-being measurement and post-study clinical laboratory safety evaluation. Laboratory assessments (haematology, biochemistry, serology and urine analysis), chest X-ray (P/A view) and ECG recordings were done at the time of screening. Clinical examination along with vital signs (axillary temperature, radial pulse rate, sitting blood pressure and respiratory rate) were recorded during screening, prior to check-in and check-out of each period. Vital signs (axillary temperature, radial pulse rate, sitting blood pressure lying blood pressure, standing blood pressure and respiratory rate) were recorded prior to dosing in each period. Vital signs (sitting blood pressure and radial pulse rate) were measured and recorded at 1.00 and 6.00 hours after dosing (within ± 40 minutes of the scheduled time, referring to the last recording) in each period. Orthostatic hypotension was assessed at 3.00 hours after dosing in each period (within ± 40 minutes of the scheduled time). A urine screen for drugs of abuse and breath test for alcohol consumption were done during check-in of

each period. Subjects were questioned for well-being at the time of clinical examination and recording of vital signs. A safety sample was collected (at or after the time of the last blood sample collection of period 02) for post-study safety assessment [haematology and biochemistry] from all dosed subjects at the end of the study.

Pharmacokinetic parameters calculated for doxepin are summarized in Table 1.

Table 1 Descriptive statistics of formulation means for doxepin obtained by a non-compartmental model (N = 40)

Pharmacokinetic Parameters (Units)	Mean ± SD (Un-transformed data)	
	Test Product (T)	Reference Product (R)
C_{max} (ng/mL)	35.5422 ± 29.59574	37.4898 ± 34.80835
AUC_{0-72h} (ng.hr/mL)	450.9084 ± 501.26900	498.9823 ± 671.66219
K_{el} (hr^{-1})	0.0388 ± 0.01016	0.0386 ± 0.00875
$t_{1/2}$ (hr)	19.3507 ± 7.11750	18.8875 ± 4.48142
T_{max} (hr)	2.275 ± 0.7675	2.325 ± 0.7970
	Median	
T_{max} (hr)	2.000	2.000

The ln-transformed geometric least squares mean of T and R, its ratio (T/R)% and 90% confidence interval (CI) of the Geometric least square mean ratio (T/R) obtained from the analysis of ln-transformed parameters C_{max} and AUC_{0-inf} of doxepin are summarized in Table 2.

Table 2 Geometric least squares means, ratios and 90% confidence intervals for pharmacokinetic parameters (C_{max} and AUC_{0-72h}) of doxepin (N = 40)

Pharmacokinetic Parameters (Units)	Ln-transformed			90% Confidence Interval (Parametric)	
	Geometric Least Squares Mean				
	Test Product (T)	Reference Product (R)	T/R (%)	Lower	Upper
C_{max} (ng/mL)	28.6689	28.8594	99.34	86.74	113.77
AUC_{0-72h} (ng.hr/mL)	346.5789	362.0302	95.73	87.70	104.50

Pharmacokinetic parameters calculated for desmethyldoxepin (Nordoxepin) are summarized in Tables 3.

Table 3 Descriptive statistics of formulation means for desmethyldoxepin (Nordoxepin) obtained by a non-compartmental model (N = 39)[a]

Pharmacokinetic Parameters (Units)	Mean ± SD (Un-transformed data)	
	Test Product (T)	Reference Product ®
C_{max} (ng/mL)	7.5079 ± 3.57422	7.5769 ± 3.50602
AUC_{0-72h} (ng.hr/mL)	308.2161 ± 156.12430	316.7909 ± 172.25802
K_{el} (hr^{-1})	0.0175 ± 0.00387	0.0167 ± 0.00417
$t_{1/2}$ (hr)	42.1725 ± 12.65482	45.2162 ± 17.51102
T_{max} (hr)	5.783 ± 2.0760	5.218 ± 2.0222
	Median	
T_{max} (hr)	5.500	5.000

[a] In Subject no. 33, the pre-dose concentration of desmethyldoxepin (Nordoxepin) observed was > 5% of the C_{max} in Period 02. Hence, the subject was excluded from pharmacokinetic and statistical analysis as per protocol.

The ln-transformed geometric least squares mean of T and R, its ratio (T/R)% and 90% CI of the Geometric least square mean ratio (T/R) obtained from the analysis of ln-transformed parameters C_{max} and AUC_{0-inf} of desmethyldoxepin (Nordoxepin) are summarized in Table 4.

Table 4 Geometric least squares means, ratios and 90% confidence intervals for pharmacokinetic parameters (C_{max} and AUC_{0-72h}) of desmethyldoxepin (Nordoxepin) (N = 40)

Pharmacokinetic Parameters (Units)	Ln-transformed			90% Confidence Interval (Parametric)	
	Geometric Least Squares Mean				
	Test Product (T)	Reference Product (R)	T/R (%)	Lower	Upper
C_{max} (ng/mL)	6.8544	6.9094	99.20	94.10	104.58
AUC_{0-72h} (ng.hr/mL)	277.7629	281.1774	98.79	94.26	103.53

Linear plot and ln-linear plot mean plasma concentrations of doxepin by time are shown in Figs 2-3.

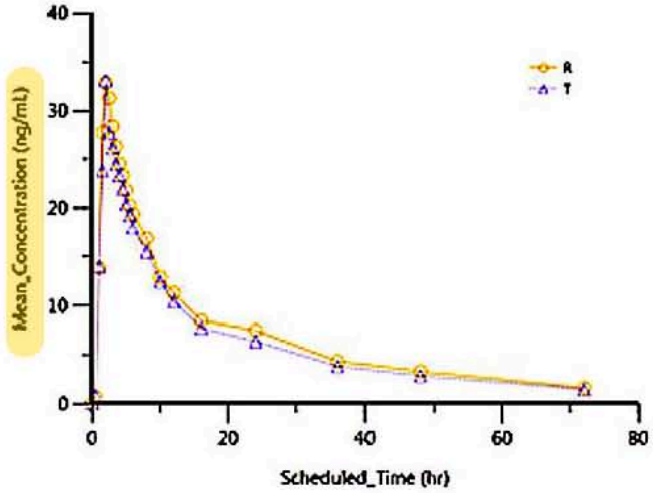

Figure 2 Linear plot of mean plasma concentrations of doxepin vs. time for Test Product (T) and Reference Product (R) (N = 40)

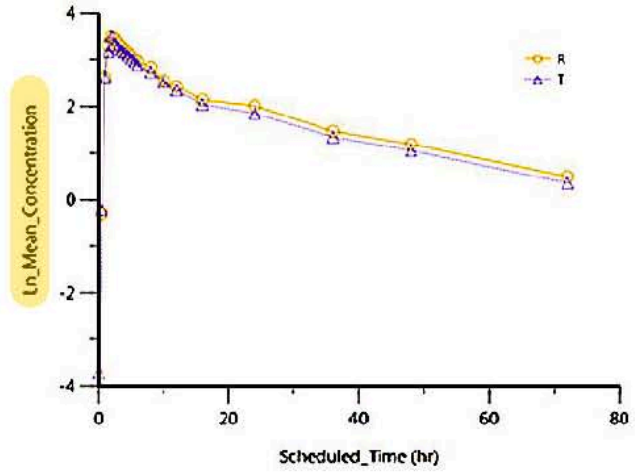

Figure 3 Ln-linear plot of mean plasma concentrations of doxepin vs. time for Test Product (T) and Reference Product (R) (N = 40)

Linear plot and ln-linear plot mean plasma concentrations of desmethyldoxepin (Nordoxepin) by time are shown in Figs 4-5.

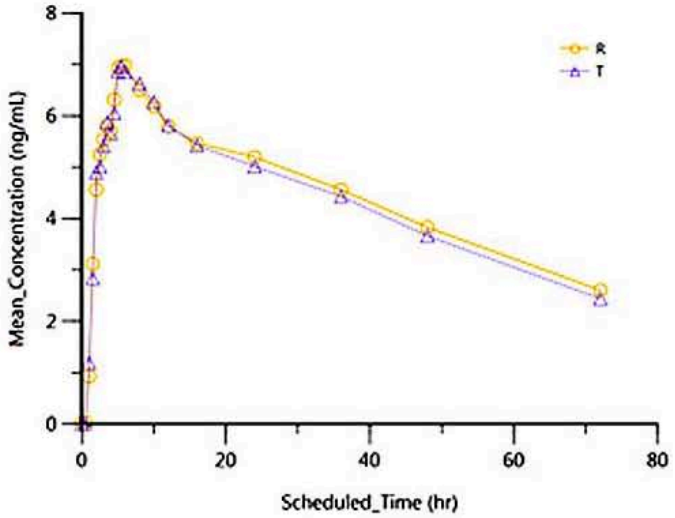

Figure 4 Linear plot of mean plasma concentrations of desmethyldoxepin (Nordoxepin) vs. time for Test Product (T) and Reference Product (R) (N = 39)

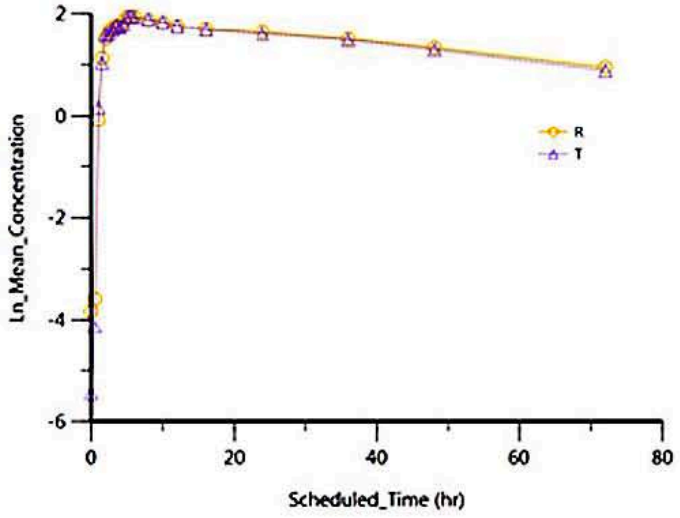

Figure 5 Ln-linear plot of mean plasma concentrations of desmethyldoxepin (Nordoxepin) vs. time for Test Product (T) and Reference Product (R) (N = 39)

Safety Results

All subjects who had received at least one dose of investigational product were included in safety evaluation. No severe, serious or life-threatening adverse events were reported during the course of the study. Seven adverse events were observed in the study, involving 06 subjects (subject nos. 04, 08, 27, 31, 33 and 34) out of 40. One adverse event was found after the administration of reference product in period 01, 01 adverse event was found after the administration of test product in period 02 and 05 adverse events were found by the post-study clinical laboratory safety evaluation (clinically significant changes in laboratory parameters).

Subject no. 08 experienced dizziness after the administration of test product (T) during period 01.
Subject no. 33 experienced dizziness after the administration of reference product (R) during period 01.

Clinically significant laboratory abnormalities (documented as adverse events) detected during the post-study clinical laboratory safety evaluation included decreased hemoglobin level (01 subject, 1.25 %), increased liver enzymes (02 subjects, 2.5%), increased eosinophils level (02 subjects, 2.5%). As this observation was detected during the post-study safety analysis, it could not be attributed to either the test (T) or the reference (R) product. Hence, adverse events associated with clinically significant post-study laboratory results were imputed to both formulations. In all cases of clinically significant abnormal post-study laboratory investigation results, the adverse events were 'mild' in intensity, and 05 was considered as possibly related and 02 was unlikely related to the study drug administered.

Subject no. 08 and 33 was followed until the resolution of their adverse event.
Subject nos. 04, 27, 31, 33 and 34 under follow-up for their post-study safety adverse events.

2.5.2.2 Comparative *In Vitro* Release Characteristics

N/A

2.5.2.3 Comparative *In Vivo* Release Characteristics

N/A

2.5.2.4 Conclusions on Biopharmaceutics and Essential Similarity

Bioequivalence of the test product (T) Doxepin 50 mg capsules of Morningside Healthcare Ltd., UK and reference product (R) Doxepin Hydrochloride BP 50 mg capsules of Marlborough Pharmaceuticals Ltd., UK in relation to the rate of doxepin absorption, can be concluded based on the result of the analysis of the doxepin data. The 90% CIs of the differences of least squares means for the pharmacokinetic parameters C_{max} (86.74% – 113.77%) and AUC_{0-72h} (87.70% – 104.50%) of doxepin as well as those for the pharmacokinetic parameters C_{max} (94.10% – 104.58%) and AUC_{0-72h} (94.26% – 103.53%) of desmethyldoxepin (Nordoxepin) are within the bioequivalence acceptance limits of 80.00 – 125.00% as set by the European Medicines Agency' (EMA) Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr) that came into effect on 1 August 2010.

Based on these results, the Test Product (Doxepin 50 mg capsules of Morningside Healthcare Ltd, UK) when compared with the Reference Product (Doxepin

Hydrochloride BP 50 mg capsules of Marlborough Pharmaceuticals Ltd., UK) meets the bioequivalence criteria in terms of rate and extent of absorption after administration of single dose under fasting conditions as set in the protocol.

Both the Test product and the Reference product were well tolerated by all subjects. No serious adverse event (SAE) or significant adverse event (AE) was observed during the entire course of the study. Therefore, the interchangeable use of the Test and Reference Product should not compromise the safety, tolerability and efficacy of doxepin treatment regimens with these specific products.

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2.5.3 Clinical Pharmacology

2.5.3.1 Pharmacokinetics

2.5.3.1.1 Absorption

The kinetics of doxepin hydrochloride was studied in 7 volunteers after the oral administration of 75 mg ([redacted]). Peak plasma concentrations of doxepin ranged from 8.8 to 45.8 ng /mL and were reached within 4 hr. The semilogarithmic plot of the mean levels of doxepin and desmethyldoxepin (DMD), a major metabolite of doxepin, of 7 subjects against time is illustrated in Fig. 6. The line of best fit during the terminal elimination phase is also shown.

Figure 6 Semilogarithmic plot of the mean plasma levels of doxepin and desmethyldoxepin against time and the least-squares regression line of the ß elimination phase (n = 7).

The disappearance of doxepin was biphasic and followed first-order kinetics. The mean doxepin half-life ($t_{½}$) was 16.8 hr (range: 8.2 - 24.5 h). The estimated first-pass metabolism of doxepin ranged from 55% to 87% of the oral dose assuming complete absorption.

The pharmacokinetics of orally administered doxepin (50 mg) was studied in 8 healthy volunteers ([redacted]). Doxepin and DMD concentrations in serum (or plasma) and red blood cells (RBCs) were measured by radioimmunoassay. Table 5 shows the mean values of the calculated kinetic parameters of doxepin and DMD in eight subjects.

Table 5 Mean pharmacokinetic parameters of doxepin and DMD after a single oral dose (50 mg) to 8 healthy volunteers.

Parameters	Doxepin	DMD
C_{max} (ng/mL)	82.3 ± 5.1	59.50 ± 9.0
T_{max} (h)	1.3 ± 0.2	3.6 ± 0.5
α (1/h)	0.432 ± 0.059	-
$t_{½α}$ (h)	2.0 ± 0.5	-
ß	0.048 ± 0.005	0.029 ± 0.06
$t_{½}$ (h)	17.9 ± 4.3	28.5 ± 3.7
$AUC_{0-\infty}$ (ng.h/mL)	870.6 ± 139.4	1276.6 ± 125.7
f	0.29 ± 0.03	-
$V^{ß}$ (L/kg)	22.7 ± 4.3	-
Cl (1/h/kg)	0.93 ± 0.03	-
Protein binding (%)	75.50.03 1.6	76.0 ± 1.6

α = slope of the distribution phase
$t_{½α}$ = distribution half-life
ß = slope of the elimination phase
$t_{½}$ = elimination half-life
f = estimate of the fraction of the oral dose not metabolized during first-pass through the liver = liver blood flow / liver blood flow + (dose/AUC)
$V^{ß}$ = total apparent volume of distribution = f x (dose / ß x $AUC_{0-\infty}$
Cl = total plasma clearance = ß x $V^{ß}$

Therapeutic response appears to correlate with plasma levels of the active metabolite DMD or of doxepin plus DMD, but not with doxepin itself.

Serum-level databank was analysed, a questionnaire was sent to US and German psychiatric university departments and laboratories, and the literature was reviewed ([redacted]). The main results were as follows: (1) Only 9% of all samples analysed (N = 217) displayed plasma levels measured by high-performance liquid chromatography (HPLC) between 150 and 250 ng/mL; 88% were subtherapeutic. The mean doxepin + DMD steady-state serum concentration was 89 ± 75 ng/mL (n =32, doxepin > 3 weeks). The mean daily dose was 143 ± 30 mg. There was no correlation between concentrations and improvement. (2) A wide variety of recommendations is given by the different university departments (10 – 1,000 ng/mL). (3) According to the studies published to date, there is not enough evidence for recommending a therapeutic range. A preliminary working range of 50 to 250 ng/mL was proposed based on critical reassessment of published data

2.5.3.1.2 Distribution

The kinetics of doxepin hydrochloride was studied in 7 volunteers after the oral administration of 75 mg ([redacted]). The mean apparent volume of distribution was 20.2 L/kg (9.1 - 33.3 L/kg).

A method was developed for quantitative measurement of histamine H_1 receptor in human brain by positron emission tomography (PET) and [^{11}C]doxepin ([redacted]). The estimated parameters with a two-compartment model were stable for the initial values for parameter estimation but those with a three-compartment model were not. Since the cerebellum has a very low density of H_1, it is reasonably considered that the specific distribution volume (DV) in the cerebellum corresponds to non-specific binding of [^{11}C]doxepin in the brain. Therefore, the difference between each DV and cerebellar DV reflects the specific binding of [^{11}C]doxepin in each region. The subtracted DVs in the other regions are shown in Fig. 7.

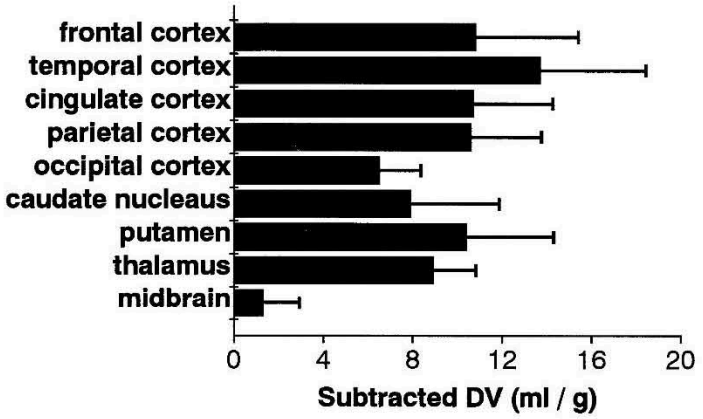

Figure 7 The specific DV of [^{11}C]doxepin in the human brain. The specific DV was determined by the difference between DV in each brain region and that in the cerebellum, and expressed the mean ± SD (n = 5).

2.5.3.1.3 Metabolism

Doxepin is extensively metabolized to N-desmethyldoxepin, which is a biologically active metabolite and other inactive metabolites. The first-pass metabolism accounts for 55-87% of the administered dose. After that, the secondary metabolism is driven by the transformation of N-desmethyldoxepin to its glucuronide conjugates ([redacted]). The main metabolic enzymes involved in the transformation of doxepin are the members of the cytochrome P450 family, CYP2C19 and CYP2D6 with minor involvement of CYP1A2 and CYP2C9.

The stereoselective metabolism of doxepin was examined *in vitro*, with the use of human liver microsomes, recombinant CYP2D6 and gas chromatography-mass spectrometry ([redacted]). In human liver microsomes, over the concentration range 5 ± 1500 μM, the rate of Z-doxepin N-demethylation exceeded that of E-doxepin above 100 μM in two of three livers. Eadie-Hofstee plots were curvilinear indicating the involvement of several enzymes in N-demethylation. Coincubation of doxepin with 7,8-naphthoflavone and ketoconazole reduced the rates of N-demethylation of E- and Z-doxepin by 30 ± 50% and 40 ± 60%, respectively, suggesting the involvement of CYP1A and CYP3A4, whilst quinidine had little effect on N-demethylation. In contrast, doxepin hydroxylation was exclusively stereospecific; E-doxepin and E-N-desmethyldoxepin were hydroxylated with high affinity in liver microsomes and by recombinant CYP2D6 (K_m in the range of 5 ± 8 μM), but there was no evidence of Z-doxepin hydroxylation. In `metabolic consumption' experiments with liver microsomes (having measurable CYP2D6 activity) and initial substrate concentration of 1 μM, the consumption of E-doxepin was greater ($p < 0.05$, $n = 5$) than that of Z-doxepin. In summary, CYP2D6 is a major oxidative enzyme in doxepin metabolism; predominantly catalysing hydroxylation with an exclusive preference for the E-isomers ([redacted]). The relatively more rapid metabolism of E-isomeric forms, and the limited metabolic pathways for the Z-isomers may explain the apparent enrichment of Z-N-desmethyldoxepin that is observed *in vivo*. The proposed metabolic scheme for doxepin is shown in Fig. 8.

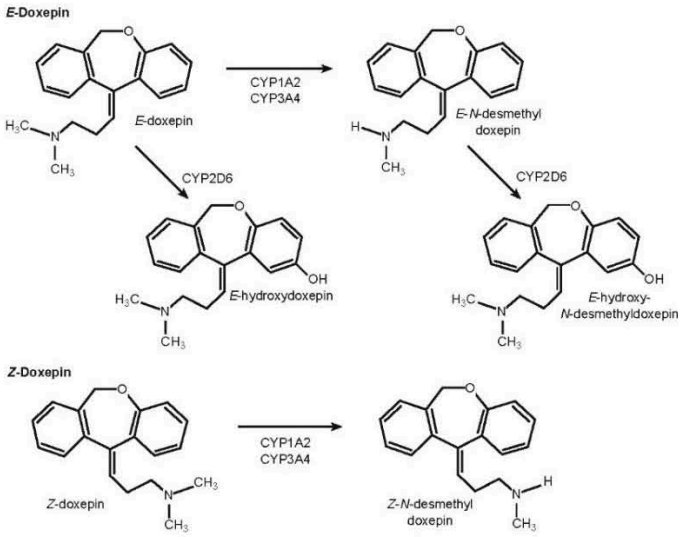

Figure 8 The metabolic pathways of doxepin and the CYP isoenzymes identified from this study as catalysing each stage. E-Doxepin may undergo hydroxylation or N-demethylation, the latter metabolite may subsequently undergo hydroxylation. In human liver microsomes, Z-doxepin is N-demethylated to a terminal metabolite.

The kinetics of doxepin hydrochloride was studied in 7 volunteers after the oral administration of 75 mg ([redacted]). Significant quantities of the metabolite DMD were produced. Peak levels of DMD ranged from 4.8 to 14.5 ng/mL and were reached between 2 and 10 hr after administration. The mean $t_{½}$ of DMD was 51.3 h that ranged from 33.2 to 80.7 h. There was no correlation between the doxepin and DMD $t_{½}$s. The amount of DMD produced correlated with the plasma concentration of doxepin and appears to explain the correlation between the steady-state concentrations of doxepin and DMD in patients given doxepin. Significant amounts of DMD were produced by *in vivo* demethylation. The peak levels of DMD occurred a mean of 6 hr after the oral dose. The rate of conversion of doxepin to DMD is related to the doxepin plasma concentration. DMD has a longer $t_{½}$, mean, 51.3 hr, than doxepin. Metabolites corresponding to the desmethyl derivative, doxepin-N-oxide, and the hydroxylated derivative plus its glucuronide, were identified in human urine ([redacted]).

2.5.3.1.4 Elimination

Urinary excretion studies in 7 healthy male volunteers, who received 25mg doxepin on Day 1 and 50 mg on Day 3, demonstrated that the excretion of doxepin and its desmethyl metabolite were < 0.5% of the administered dose ([redacted]). Excretion was greatest after a 50 mg dose, with most occurring during the periods 4 to 6 and 6 to 12 hours after oral administration. The mean elimination $t_{½}$ was 16.8 h and the oral dose of doxepin was extensively metabolized during the first pass through the liver

2.5.3.2 Pharmacokinetics in Special Populations

2.5.3.2.1 Renal Impairment

For doxepin, the various pharmacokinetic parameters were similar among patients with advanced chronic kidney disease (CKD) and healthy controls. Interindividual variability of pharmacokinetic parameters of doxepin is high ([redacted]). No adjustment in dose is recommended by the European Renal Best Practice ([redacted]).

2.5.3.2.2 Hepatic Impairment

Doxepin is extensively metabolized by the liver ([redacted]). Their plasma clearance may be decreased and their half-life prolonged in patients with impaired hepatic function. Therapy with doxepin should be administered cautiously in patients with liver disease, and the dosage should be adjusted accordingly.

2.5.3.2.3 Age

Metabolism of doxepin may be diminished in elderly patients, leading to a longer terminal half-life and possibly a longer duration of action ([redacted];

[redacted]). There are age-related decrease in systemic clearance and potential changes in pharmacokinetic drug-drug interactions ([redacted]).

2.5.3.2.4 Gender

Clinical trials have included both male and female patients and no pharmacokinetic alterations specific to gender have been reported.

2.5.3.2.4 Race

No race related pharmacokinetic alterations have been reported.

2.5.3.3 Clinically Relevant Pharmacokinetic Interactions

Drugs Metabolized by P450 2D6

The biochemical activity of the drug metabolizing isozyme cytochrome P450 2D6 (debrisoquin hydroxylase) is reduced in a subset of the Caucasian population (about 7% to 10% of Caucasians are so called "poor metabolizers"); reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African and other populations are not yet available ([redacted]). Poor metabolizers have higher than expected plasma concentrations of tricyclic antidepressants (TCAs) when given usual doses ([redacted]). Depending on the fraction of drug metabolized by P450 2D6, the increase in plasma concentration may be small, or quite large (8-fold increase in plasma AUC of the TCA). Inhibitors or substrates of CYP2D6 (e.g. quinidine, selective serotonin reuptake inhibitors) may increase the plasma concentration of doxepin when administered concomitantly. The extent of interaction depends on the variability of effect on CYP2D6. The clinical significance of this interaction with doxepin has not been systematically evaluated.

MAO Inhibitors

Combined use with other antidepressants, alcohol or antianxiety agents should be undertaken with due recognition of the possibility of potentiation. It is known, for example, that monoamine oxidase inhibitors may potentiate other drug effects; therefore, doxepin should not be given concurrently, or within two weeks of cessation of therapy, with monoamine oxidase inhibitors ([redacted]). Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors ([redacted]). Therefore, MAO inhibitors should be discontinued at least 2 weeks prior to the cautious initiation of therapy with doxepin. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Cimetidine

Cimetidine significantly inhibits the biotransformation of doxepin, and has been reported to produce clinically significant fluctuations in steady-state serum concentrations of various tricyclic antidepressants ([redacted]). Serious anticholinergic symptoms (i.e., severe dry mouth, urinary retention and blurred vision) have been associated with elevations in the serum levels of tricyclic antidepressant when cimetidine therapy is initiated.

Antihypertensive drugs

Doxepin may decrease the antihypertensive effect of agents such as debrisoquine, bethanidine, guanethidine and possibly clonidine ([redacted]). It usually requires daily doses of doxepin in excess of 150mg before any effect on the action of guanethidine is seen. It would be advisable to review all anti-hypertensive therapy during treatment with tricyclic anti-depressants.

Antiepileptic drugs

Antiepileptic drugs (carbamazepine, phenobarbital, phenytoin and primidone) may increase the rate of metabolism of doxepin. Plasma concentrations and therapeutic effects of tricyclic antidepressants may be decreased during concurrent use with barbiturates because of increased metabolism resulting from induction of hepatic microsomal enzymes ([redacted]). Valproic acid can increase the blood level of doxepin. When a combination of valproic acid with doxepin is administered, cautious dosing is advisable and therapeutic drug monitoring should be performed ([redacted]).

Sublingual nitroglycerin

Tricyclic antidepressants (amitriptyline, desipramine, doxepin, others) and anticholinergic drugs may cause dry mouth and diminished salivary secretions ([redacted]; [redacted]). This may make dissolution of sublingual nitroglycerin difficult.

Thyroid hormone replacement

Coadministration of thyroid hormone replacement therapy with tricyclic antidepressants may accelerate the onset or potentiate the action of tricyclic antidepressants, increasing the risk of cardiac arrhythmias and central nervous system (CNS) stimulation ([redacted]). The proposed mechanism may be an increased receptor sensitivity to catecholamines. Some clinicians have used this interaction therapeutically. However, individual cases of paroxysmal tachycardia, hypothyroidism, and thyrotoxicosis have also been reported

2.5.3.4 Pharmacodynamics

2.5.3.4.1 Pharmacology and Mode of Action (Primary Pharmacodynamics)

Doxepin is the most potent antihistamine of the tricyclic antidepressants, with four times the potency of amitriptyline and 800 times the potency of diphenhydramine at the H_1 receptor ([redacted]; [redacted]). At standard antidepressant doses (> 75 mg/day), doxepin inhibits the reuptake of serotonin ([redacted]) and norepinephrine and antagonizes cholinergic, histaminergic, and α-adrenergic activity ([redacted]). Doxepin is a moderately potent competitive inhibitor of serotonin uptake in human blood platelets *in vitro*, with an inhibitory constant (K_i) of about 2 x 10^{-7} M ([redacted]).

H_1 receptor binding

[^{11}C]Doxepin binding was tested between morning and afternoon and between resting and attentive waking conditions in healthy human subjects ([redacted]). There was a trend for a decrease in [^{11}C]doxepin binding during attentive calculation tasks compared with that in resting conditions, but the difference (< 10%) was not significant. Similarly, the binding potential of [^{11}C]doxepin in the cerebral cortex was slightly higher in the morning than that in the afternoon, but it was also insignificant. These data suggest that higher histamine release during wakefulness could not decrease the [^{11}C]doxepin binding in the human brain. H_1 receptor binding was highest in the cingulated cortex ([redacted]). The prefrontal cortex and temporal cortex also showed relatively high binding ratios, whereas in the cerebellum, binding was very weak and was rarely specific. The crystalline structure of the human H_1 receptor complex with doxepin revealed a specific interaction with the H_1 receptor protein and doxepin.

Effect on serotonin uptake

The effect of doxepin on uptake and efflux of serotonin was studied in human blood platelets *in vitro* ([redacted]). The inhibitory effect was 6 times stronger in an artificial, protein-free medium than in diluted plasma, corresponding to about 85% protein binding. The efflux of serotonin from platelets preloaded with ^{14}C-serotonin was not affected by doxepin in concentrations up to 10^{-6} M, but increased rapidly at concentrations above 10^{-4} M (Fig. 9).

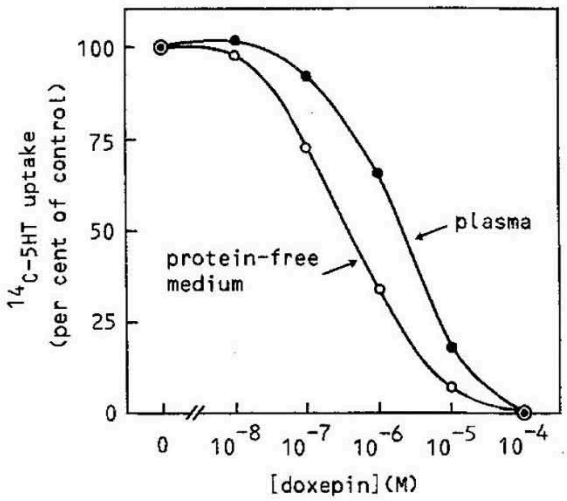

Figure 9 Inhibitory effect of doxepin on serotonin uptake in diluted platelet rich plasma (●) and in artificial protein-free medium (○). Platelets incubated with ^{14}C-serotonin 0.5 nM for 4 min. Uptake given as percent of controls without drug. Each point represents mean of 12 parallel samples

As a hypnotic, doxepin is used at low doses (< 10 mg/day), in which case it theoretically affects only the histamine receptor, with no meaningful effects on the noradrenergic and serotonergic systems.

Effect on adrenergic transmission

Fourteen depressed patients were treated for 1 to 8 weeks (4.1 ± 0.6, mean ± SEM) with imipramine, doxepin, or amitriptyline to study the effects of tricyclic antidepressants on sympathetic nervous system (SNS) function ([redacted]). Supine plasma NE and epinephrine levels, mean arterial blood pressure (MAP), and heart rate were measured at rest, after standing, and during graded, supine maximal bicycle exercise. After tricyclic antidepressants, NE was increased by 51 ± 6% of basal values and heart rate rose, but epinephrine and MAP were unchanged. The supine to 10-min standing increment in NE increased from 309 ± 51 pg/mL at baseline to 406 ± 55 pg/mL during TCA treatment.

Anticholinergic activity

Peripheral anticholinergic activity of single acute doses of doxepin 100 mg and placebo was assessed by several physiologic measures in normal male volunteers ([redacted]). Doxepin produced significant depressions in salivary flow and finger sweating compared to placebo. The anticholinergic activity in serum of depressive patients receiving doxepin (50–225 mg/day) was measured using a radioreceptor assay ([redacted]). The steady state serum levels of doxepin and its desmethylated metabolite, DMD were measured by radioimmunoassay in the same serum samples.

The antimuscarinic activity in serum measured as atropine equivalents was 1.1 ± 0.2 ng/ml in doxepin patients.

2.5.3.4.2 Secondary Pharmacodynamics

Treatment of oral mucositis–related pain

The effect of doxepin mouthwash or diphenhydramine-lidocaine-antacid mouthwash was evaluated for the treatment of oral mucositis–related pain in a Phase 3 randomized trial that included 275 patients who underwent definitive head and neck radiotherapy, had an oral mucositis pain score of 4 points or greater (scale, 0-10), and were followed up for a maximum of 28 days ([redacted]). Mucositis pain during the first 4 hours decreased by 11.6 points in the doxepin mouthwash group, by 11.7 points in the diphenhydramine-lidocaine-antacid mouthwash group, and by 8.7 points in the placebo group. Among patients undergoing head and neck radiotherapy, the use of doxepin mouthwash significantly reduced oral mucositis pain during the first 4 hours after administration. In another study, 155 patients were randomly allocated to a doxepin oral rinse or a placebo for the treatment of radiotherapy-related oral mucositis pain ([redacted]). Crossover analysis of patients completing both phases confirmed that patients experienced greater mouth and throat pain reduction with doxepin (intrapatient changes of 4.1 for doxepin-placebo arm and -2.8 for placebo-doxepin arm; $p < 0.001$).

Anti-itching treatment

The topical treatment with doxepin (5%) was evaluated ACH-induced itch and cutaneous sensations (erythema, wheal, axon-reflex flare) ([redacted]). Eleven patients with atopic eczema were included in this double-blind study. Doxepin cream was applied for 3 days to a defined area on the volar forearm and basic ointment to the other side 4 times daily. Vasoreactions and cutaneous sensations were measured. Doxepin treatment over 3 days reduced ACH provoked flare size more than 53% ($p < 0.005$) and wheal size about 48% ($p < 0.005$) whereas the maximal antipruritic effect was similar to the basic therapy.

Urticaria treatment

Doxepin hydrochloride was evaluated in a double-blind, placebo-controlled crossover trial for the treatment of chronic idiopathic urticaria in 16 adults ([redacted]). Doxepin-treated subjects experienced fewer lesions ($p < 0.001$), less waking hours with lesions ($p < 0.01$), lesser degree of itch and/or discomfort ($p < 0.001$), and less swelling or angioedema ($p < 0.001$) as compared to placebo-treated subjects. Doxepin-treated subjects required less daily concomitant antihistamine use (mean 0.13 tablets versus 1.48 tablets, $p < 0.05$). Doxepin also significantly suppressed histamine- and codeine-induced cutaneous wheal response as compared to placebo.

Analgesic activity

The analgesic efficacy of topical administration of 3.3% doxepin hydrochloride, 0.025% capsaicin and a combination of 3. 3% doxepin and 0.025% capsaicin for 4 weeks was assessed in human chronic neuropathic pain in a randomized, double-blind, placebo-controlled study of 200 consenting adult patients ([redacted]). Overall pain was significantly reduced by doxepin, capsaicin and doxepin/capsaicin to a similar extent. The analgesia with doxepin/capsaicin was of more rapid onset. Burning pain was increased by doxepin and by capsaicin and to a lesser extent by doxepin/capsaicin. Side effects were minor.

Treatment of insomnia

The effect of doxepin on fatigue was investigated in a three-arm six-week randomized pilot study that included 18 patients ([redacted]). Compared to placebo, doxepin improved the Insomnia Severity Index (-9 ± 5.4 vs. -2 ± 3.9, p = 0.03), the SCOPA-night score (-5.2 ± 1.5 vs. _2.3 ± 2.8, p = 0.049), the Pittsburgh Sleep Quality Index-sleep disturbances subscale (-0.5 ± 0.5 vs 0.2 ± 0.4, p = 0.02), and both patient and examiner-rated clinical global impression of change (1.7 ± 0.8 vs. 0.5 ± 0.8, p = 0.03 and 1.4 ± 0.5 vs. 0.3 ± 0.5, p = 0.003). On secondary outcomes doxepin reduced the fatigue severity scale (p = 0.02) and improved scores on the Montreal Cognitive Assessment (p = 0.007). Non-pharmacological treatment reduced the Insomnia Severity Index (-7.8 ± 3.8 vs. -2.0 ± 3.9, p = 0.03), and the examiner-reported clinical global impression of change (p = 0.006), but was associated with decline in Parkinson Disease Questionnaire-39.

Effect on autonomic system dysfunction

The effects of doxepin and scopolamine plus amphetamine were evaluated on susceptibility and adaptability during the chronic stressful motion of microgravity ([redacted]). Daily exposure to cross-coupled angular acceleration for 5 consecutive days demonstrated that the efficacy of doxepin and scopolamine plus amphetamine in the prevention of autonomic system dysfunction was not only apparent on the first test day ($p < 0.01$), but was also evident in the substantially enhanced resistance developed over the 5-day test period ($p < 0.01$) as compared with placebo. This indicates that daily use of these medications does not diminish therapeutic efficacy (tolerance). Comparable efficacy after doxepin loading for 4 hours, 3 days, or 21 days suggests a mechanism distinct from its antidepressant effects, possibly related to its potent antihistaminergic actions.

Efficacy in irritable bowel syndrome

The efficacy of tricyclic antidepressants (TCAs) as a therapeutic option for irritable bowel syndrome (IBS) was evaluated through meta-analysis of randomized controlled trials from 1966 until September 2008 ([redacted]). It is concluded that low

dose TCAs exhibit clinically and statistically significant control of IBS symptoms. The least anticholinergic effects (i.e. doxepin and desipramine) were suggested for elderly patients or constipation-predominant IBS and imipramine or amitriptyline for diarrhea-predominant IBS and patients with insomnia.

Antiulcer therapy

In the double-blind study of 51 patients with duodenal ulcer, the effect of doxepin and placebo was evaluated ([redacted]). Complete healing of the ulcer was found in 19 of 23 patients after 4 weeks of treatment with 50 mg doxepin (83%) and in 14 of 27 patients given placebo (52%) ($p < 0.05$). Two patients in the placebo group developed complications necessitating surgical intervention. No serious side effects were registered in the doxepin group.

Effect on arousability

The arousability threshold and fall risk upon awakening of doxepin (6 mg) versus zolpidem (10 mg) were compared in a double-blind, placebo-controlled, four-way crossover study including 52 healthy adult males ([redacted]). Arousability was measured using an auditory awakening threshold delivered at the peak-plasma concentration for the active hypnotics and at matched times for the respective placebo conditions. Fall risk during the night was measured following awakening using the Berg Balance Scale and the Tandem Walk Task. Both arousability and fall risk were lower in the doxepin condition compared to the zolpidem condition. Furthermore, arousability and fall risk for doxepin did not differ significantly from the placebo conditions. A significantly greater proportion of participants in the zolpidem condition (63.5%) did not wake until receiving the loudest tone (110 dB) as compared to the doxepin (17.6%) and placebo conditions (17.3%, 5.8%). These results suggest that zolpidem has greater risks for balance and awakening threshold compared with low-dose doxepin.

2.5.3.4.3 Safety Pharmacology

Cardiovascular effects

The overall incidence of hypotension associated with doxepin therapy has been given as 2.62% in 495 patients, in whom baseline and serial blood pressure readings were made during continuous doxepin treatment ([redacted]). There has been no evidence for any increased risk of hypotensive effects of doxepin in elderly patients. In a group of healthy geriatric patients with memory deficits and behavioural problems, doxepin 25 to 150mg daily (mean 81.25mg) given at bedtime did not cause any adverse changes in EKG parameters ([redacted]). During the 12-week placebo-controlled trial, 1 patient with atrial fibrillation tolerated doxepin well while 3 patients with premature ventricular beats actually improved during doxepin treatment. Controlled trials in

depressed or anxious patients with cardiovascular disorders have shown doxepin to be well tolerated.

The highest recommended dose (6 mg) and a supratherapeutic amount (50 mg) of doxepin were assessed on cardiac repolarization under steady-state conditions in healthy adult subjects ([redacted]). A total of 206 healthy subjects (108 women, 98 men) were randomized to a study group; 192 subjects (93.2%) received all scheduled administrations of study drug, and 190 subjects (92.2%) completed the study. Neither amount of administered doxepin increased in individually corrected QT (QTcI), nor did the upper bound of the 95% Cis for the point estimates exceed 10 milliseconds at any time point. The predicted placebo-corrected change in QTcI at the mean doxepin C_{max} values for both administered amounts (6 mg: –0.88 millisecond [upper CI: 0.37 millisecond]; 50 mg, 2.38 milliseconds [upper CI: 4.00 milliseconds]) did not suggest an effect on cardiac repolarization, and no doxepin-treated subject met specific criteria for outlying QTc values.

In a double-blind placebo- and standard-controlled study designed to determine the autonomic effects of various antidepressant drugs, doxepin (50 mg and 75 mg) produced decreases in systolic and diastolic blood pressures ([redacted]). In contrast, doxepin did not produce significant effects on systolic, diastolic or mean arterial blood pressure related to postural change, however, three subjects complained of symptoms compatible with orthostatic hypotension after doxepin 75 mg. Doxepin did not produce significant effects on systolic, diastolic or mean arterial blood pressure related to postural change, but three subjects complained of symptoms compatible with orthostatic hypotension after doxepin 75 mg.

CNN effects

In single-dose studies, doxepin has demonstrated electroencephalogram (EEG) characteristics of both tricyclic antidepressants and anxiolytic drugs of the diazepam type ([redacted]). In patients with anxiety, doxepin 100 to 300mg daily produced increases in theta activity and low voltage desynchronised activity without increasing fast activity, and was associated with the development of delta activity. In healthy volunteers, doxepin (0.27 to 0.36mg/kg, IM) produced increases in delta, theta and 24-35Hz activities, and decreases in amplitude and amplitude variability, and alpha bands.

Respiratory effects

In a double-blind crossover trial, 6 healthy volunteers received doxepin (0.3mg/kg, IM). The effects of doxepin alone on carbon dioxide stimulus curves were not significantly different from those of diazepam or hydroxyzine, and the classic respiratory depressant effects of meperidine were significantly reduced when given in

combination with doxepin. However, respiratory depression can be severe in cases of massive doxepin overdosage ([redacted]). At therapeutic doses, in one study, doxepin appeared to have no adverse effect on lung function in treated patients with bronchial asthma, although in the course of a therapeutic trial, doxepin exacerbated bronchospasm in three treated chronic asthmatics. Thus, doxepin, as with other drugs with sedative properties, should be used with caution in patients with chronic obstructive lung disease.

Gastrointestinal effects

In a double-blind placebo- and standard-controlled study designed to determine the autonomic effects of various antidepressant drugs, doxepin (50 mg and 75 mg) produced statistically significant decreases in salivary flow relative to placebo, and these effects were still present 24 h after taking medication ([redacted]).

2.5.3.4.4 Clinically Relevant Pharmacodynamic Interactions

Doxepin should not be used together with, or within two weeks of therapy with monoamine oxidase inhibitors ([redacted]). Tricyclic antidepressants may antagonise the action of reserpine and adrenergic neuron blocking drugs (e.g. guanethidine, debrisoquine, bethanidine, and methyldopa) and control of blood pressure may be lost; there is some evidence to suggest that this effect may be less of a problem with doxepin than with other tricyclic drugs.

Increased sedative effects may occur when doxepin is used concurrently with antihistamines, hypnotics, tranquillisers, narcotics (no increase in analgesia). Tolerance to alcohol may be lowered ([redacted]). Concurrent use of alcohol or other CNS depression-producing agents with doxepin may result in serious potentiation of CNS depression, respiratory depression, and hypotensive effects ([redacted]). General anaesthetics and local anaesthetics (containing sympathomimetics) given during tricyclic or tetracyclic anti-depressant therapy may increase the risk of arrhythmias and hypotension, or hypertension. If surgery is necessary, the anaesthetist should be informed that a patient is being so treated ([redacted]).

Increased anticholinergic effects may occur when doxepin is used concurrently with drugs possessing anticholinergic activity (e.g., gastrointestinal (GI) antispasmodics, some antihistamines and antiparkinsonian drugs). The dosage requirements of a tricyclic antidepressant may be lowered in patients also receiving therapy with thyroid drugs. The risk of toxic effects may be increased in elderly patients and in those with myxoedema or cardiovascular disease. Doxepin should not be given with sympathomimetic agents such as ephedrine, isoprenaline, noradrenaline, phenylephrine and phenylpropanolamine.

MODULE 2 OVERALL SUMMARIES

2.5 Clinical Overview

2.5.4 Overview of Efficacy

2.5.4.1 Efficacy in Depression

A double-blind parallel-group comparison study of moclobemide versus doxepin was performed in 237 patients with major depression ([redacted]). Moclobemide was equal in efficacy and better tolerated than doxepin. Moclobemide therapy more often than doxepin resulted in increased sexual desire. An exploratory analysis of UKU-measured symptoms of impaired sexual function prior to commencement of the study revealed that moclobemide more often than doxepin led to an improvement of reduced libido and impaired erection, ejaculation and orgasm.

In a double-blind parallel group 6-week study, in which the selective MAO-A inhibitor moclobemide (max. dose 600 mg) was compared with doxepin (max. dose 250 mg), 56 patients attending a general practitioner for treatment of depression, most of whom met the criteria for major depression, were included ([redacted]). Thirty patients on moclobemide and 23 on doxepin were assessed after treatment for at least 1 week primarily with the Montgomery-Asberg Depression Rating Scale (MADRS). Overall improvement measures showed a nonsignificant difference in favour of doxepin. Previous or present panic attacks (10 patients in the moclobemide group and – by chance – only one in the doxepin group) were associated with significantly lower improvement within the moclobemide group. Improvement was negatively correlated with age; this was statistically significant in the total group as well as in the moclobemide group, with a nonsignificant trend in the same direction in the doxepin group.

In a double-blind parallel group study, the efficacy and safety of amitriptylinoxide were evaluated vs. doxepin in the treatment of in-patients with severe depression ([redacted]). Two groups of 22 patients each received amitriptylinoxide and doxepin respectively at a daily dosage of 120–360 mg for a period of 4 weeks. The total score on the Hamilton Depression Scale (HAMD) was reduced with amitriptylinoxide on an average from 28 ± 5 before treatment to 12 ± 8 at the end of treatment, with doxepin from 29 ± 8 to 13 ± 11. Of the amitriptylinoxide-treated patients, 12 showed a more than 50 % reduction in this score compared with 15 under doxepin. The difference was not statistically significant.

In a double-blind clinical trial, 163 patients with major depression were randomly assigned to treatment with mirtazapine or doxepin for 6 weeks ([redacted]). Initially, patients received mirtazapine 20 mg/day or doxepin 75 mg/day, dosages were

then titrated up to a maximum of 60 mg/day and 300 mg/day, respectively. Both drugs produced considerable improvement in depressive symptoms with no statistically significant differences between the two patient groups. In the mirtazapine group, only two patients prematurely terminated the study due to adverse drug experiences, as compared to six in the doxepin-treated group. Moreover, doxepin-treated patients complained more frequently of dry mouth and movement disorders.

A double-blind controlled study comparing the effects of bupropion (300 to 450 mg/kg) to doxepin (100 to 225 mg/kg) during a 13-week treatment period in outpatients with primary depression was conducted to evaluate efficacy and safety differences between the two drugs ([redacted]). Following a 7-day placebo washout period, patients could be treated for up to 13 weeks on either treatment. Antidepressant response was assessed by the Hamilton Depression and Anxiety Scales, Clinical Global Severity and Improvement Ratings, and the Zung Self-Rating Depression Scale. Comparable efficacy between the compounds was found across the 13-week study. Doxepin differed from bupropion mainly on the sleep factor of the Hamilton Depression Scale, with doxepin improving sleep to a greater extent than bupropion. Doxepin produced a greater incidence of anticholinergic side effects, including dry mouth, constipation, sleepiness, and tiredness, in comparison to bupropion. In addition, increased appetite and weight gain were consistent side effects of doxepin relative to bupropion.

The efficacy of daily low doses (10 to 20 mg) of doxepin in the treatment of depressive disorders in elderly inpatients was assessed by a double-blind study in 24 patients ([redacted]). The patients were treated for a 3-week period to test for an early response. Hamilton Depression Rating Scale (HDRS) and Geriatric Depression Scale were used to quantify symptoms of depression. The patients treated with doxepin had a significantly greater reduction in depressive symptoms than did those who received a placebo. No side effects were found and there were no major differences in the degree of physical dependency between the doxepin and placebo groups. A depressive disorder is a common occurrence among elderly inpatients and the effectiveness of low dose doxepin therapy without demonstrable side effects argues for the active treatment for this condition.

Clovoxamine (150 – 300 mg), a neuronal serotonin and noradrenaline uptake inhibitor, was compared with doxepin (75 – 100 mg) in depressed patients over four weeks in a multicentre double-blind controlled study ([redacted]). Antidepressant efficacy was comparable for both drugs, but clovoxamine might have a special degree of efficacy for patients with more severe depressive illnesses.

In a 5-week randomized, double-blind comparative study, 49 patients with primary affective disorder were treated with doxepin (50 – 200 mg daily) and desipramine (50 – 200 mg daily) following a 1-week placebo washout period ([redacted]). Weekly ratings were obtained by HDRS, Raskin-Covi Scale, a Physician's Sleep Questionnaire, and the Asberg Side Effect Scale. Although the patient improvement for both drugs was similar at Weeks 1 and 4 of drug therapy, doxepin did appear to work significantly faster than desipramine, with statistically significant differences in HDS after weeks 2 and 3 ($p < 0.001$, and $p < 0.05$, respectively). Additionally, doxepin demonstrated a significantly more rapid improvement on specific HDS items. While both drugs equally improved initial, middle, and delayed insomnia scores by week 4, doxepin did show a significantly more rapid effect on the scores of the three HDS sleep items than DMI at Weeks 1 and 2 ($p < 0.01$ and $p < 0.04$, respectively).

Maprotiline and doxepin were compared in the treatment of depression in a double-blind multicentre trial ([redacted]). Four centres and 95 in- and out-patients took part in the trial. The severity of depression was evaluated with the aid of a visual analogue scale and nine target symptoms. Both maprotiline and doxepin diminished neurotic as well as psychotic depression significantly. The mean time of onset of action was 7.0 days in the maprotiline group and 7.7 days in the doxepin group. No statistically significant differences in antidepressive effect were found between the treatments. Two patients in the maprotiline group and four patients in the doxepin group discontinued the treatment because of unwanted effects, one patient in each group because of lack of efficacy.

In a four-week, double-blind, clinical trial, 31 patients with depressive neurosis were treated with viloxazine, doxepin, or placebo ([redacted]). On the basis of clinical interviews, the Brief Psychiatric Rating Scale (BPRS), the Witten born Psychiatric Rating Scale (WITT), and the Clinical Global Impression (CGI) were completed at baseline and when the patient com pleted the study. The Hamilton Psychiatric Rating Scales for Depression and Anxiety (HAMD and HAMA) were completed before the patient began medication, weekly, and at termination. The patient completed the Zung Self-Rating Depression Scale (SDS) at baseline, weekly, and at termination. There were no differences among the three groups in therapeutic effects. Many depressed outpatients improve on placebo.

The effectiveness of doxepin on depressed patients was compared with amitriptyline in 55 subjects by a double-blind, matched pair method ([redacted]). Sequential analysis was used mainly and a comparison of both drug groups was done to analyse the effectiveness on each symptom and the side-effects. After 1-week treatment, no significant score changes were found in the doxepin group in depressive symptoms and

neurotic symptoms. In hypochondriasis, however, the score changes were significant in the doxepin group.

In a randomized double-blind placebo-controlled study, the effect of the switch from parenteral to oral administration of doxepin on symptoms of endogenous depression was evaluated ([redacted]). Precondition was a selection of patients with typical "endogenous" depressions and maintenance of at least constant plasma levels of the active antidepressants. In patients under the age of 65 years, worsening of conditions can generally be achieved by switching in a ratio of 125 mg, IV to 250 mg/PO in the case of doxepin. Individual case studies indicated that a worsening in the patient's progress after switching was correlated with a decreasing plasma level of the active drug. Low plasma level already during the infusion period, insufficient response, and questionable compliance on oral medication were associated. Due to large interindividual differences of plasma levels by a factor of 10, measurements before and after switching are required.

Thirty-six depressed ambulatory patients were treated with doxepin or fluoxetine in a double-blind, randomized 6-week trial with placebo run-in ([redacted]). Seven patients treated with doxepin and 13 patients treated with fluoxetine met diagnostic criteria for melancholic depression. Average daily dose was 169.4 ± 41.6 mg for doxepin and 36.8 ± 18 mg for fluoxetine. Fifty percent response rate was observed in both treatment groups, using as outcome criterion reduction of Hamilton Depression Scale Score to < 10. Fluoxetine was equally effective as doxepin in the group of melancholic outpatients.

2.5.4.2 Efficacy in Depression Associated with Sleep Disturbances

In a randomized, double-blind, parallel-group, placebo-controlled trial, patients meeting DSM-IV-TR criteria for primary insomnia were randomized to 35 days of nightly treatment with doxepin 3 mg (n=75), doxepin 6 mg (n=73), or placebo (n=73), followed by 2 nights of single-blind placebo to evaluate discontinuation (DC) effects ([redacted]). Compared with placebo, doxepin 3 and 6 mg significantly improved wake time after sleep onset (WASO) on N1 (3 mg and 6 mg; $p < 0.0001$), N15 (3 mg P=0.0025; 6 mg P=0.0009), and N29 (3 mg P=0.024p P = 0.0007), and total sleep time (TST) on N1 (3 mg and 6 mg P<0.0001), N15 (6 mg P=0.0035), and N29 (3 mg p = 0.0261; 6 mg P < 0.0001). In terms of early morning awakenings, doxepin 3 and 6 mg demonstrated significant improvements in SE in the final quarter of the night on N1, N15, and N29, with the exception of 3 mg on N29 (P=0.0691). Rates of discontinuation were low, and the safety profiles were comparable across the 3 treatment groups. There were no significant next-day residual effects, and there were no spontaneous reports of memory impairment, complex sleep behaviours,

anticholinergic effects, weight gain, or increased appetite. Additionally, there was no evidence of rebound insomnia after doxepin discontinuation.

In a randomized, double-blind, placebo-controlled outpatient trial, elderly adults meeting DSM-IV-TR criteria for primary insomnia were randomized to four weeks of nightly treatment with either doxepin 6 mg (n = 130) or placebo (PBO; n = 124) ([redacted]). Patient-reported endpoints included subjective total sleep time (sTST), subjective wake after sleep onset (sWASO), latency to sleep onset (LSO), sleep quality, and a Patient Global Impression (PGI) scale. Doxepin 6 mg produced significantly more sTST and less sWASO at week 1 ($p < 0.0001$ both) than placebo. These significant improvements versus placebo were maintained at weeks 2–4 ($p < 0.05$). There were no significant differences in LSO for doxepin 6 mg versus placebo. Doxepin 6 mg significantly improved sleep quality (weeks 1, 3, and 4, $p < 0.05$) and several outcome-related parameters, including several items on the PGI, the severity and improvement items of the Clinician Global Impression (CGI) scale (Weeks 1 and 2) and the Insomnia Severity Index (ISI; weeks 1–4), all versus placebo.

The efficacy and safety of low-dose doxepin were investigated for insomnia in depressed patients in a retrospective case series analysis of the files of 17 inpatients diagnosed with major depressive disorder (MDD) and comorbid insomnia between January 1, 2011, and October 1, 2012 ([redacted]). Patients who had received a course of off-label doxepin (< 25 mg/day) were analysed with regard to dose, efficacy, and safety for up to 4 weeks of treatment. HDRS sleep item scores were used to estimate efficacy. The results showed no improvement in sleep onset and sleep maintenance insomnia in patients with MDD during the 4 weeks of treatment, however, a significant improvement was found in insomnia between baseline and Week 3 when considering all 3 HDRS sleep items (p = 0 .058).

The efficacy and safety of doxepin 1, 3, and 6 mg was evaluated in 67 patients with chronic primary insomnia (DSM-IV) who were randomly assigned to one of four sequences of 1 mg, 3 mg, and 6 mg of doxepin, and placebo in a crossover study ([redacted]). Wake time during sleep, the a priori defined primary endpoint, was statistically improved at the doxepin 3 mg and 6 mg doses versus placebo.

2.5.4.3 Efficacy in Depression with Associated Anxiety

Trimipramine was compared with doxepin, with respect to antidepressant, anxiolytic and cardiovascular effects in hospitalised patients with major depression and anxiety in a randomised, double-blind study ([redacted]). Both drugs improved the quality of sleep, with trimipramine proving superior in HDRS sleep disturbance factor at Week 4. Furthermore, drowsiness was not reported by these patients.

The cardiac safety and therapeutic efficacy of trimipramine and doxepin were compared in a 1-week single-blind placebo period followed by a 5-week randomized double-blind parallel group out-patient clinical trial in 37 young-elderly patients with a diagnosis of Major Depressive Episode (DSM-III criteria) ([redacted]). Placebo for 1 week was folloed by 2 weeks of titration with either drug in the dosage range of 75 mg/day up to a maximum of 200 mg/day. Both drugs were equally effective in relieving symptoms of depression and anxiety. The cardiovascular effects of both drugs were minimal.

A double-blind group comparative trial was performed comparing mianserin (10 mg) and doxepin (25 mg) in the treatment of depression with anxiety ([redacted]). Sixty outpatients from two centres were divided into 'high' and 'low' severity groups, based on initial HRS scores, and treated for four weeks. Standard rating scales for depression and anxiety demonstrated a substantial improvement with both drugs. However, no consistent difference in efficacy was found although the 'low severity' group appeared to respond better to mianserin.

In a double-blind study on 40 outpatients (20 per group) suffering from endogenous and psychogenic depression of the anxious-agitated or inhibited form, trazodone was compared with doxepin to determine their efficacy and safety, and whether a single daily administration was adequate ([redacted]). Increasing doses of trazodone 50-200 mg and doxepin 25-100 mg were given once a day (QD) in the evening for a period of 5 weeks. Both drugs were found to be approximately equivalent as far as their antidepressive and anxiolytic effects and safety are concerned.

In a 6-week randomized double-blind study, the therapeutic effect and safety of alprazolam and doxepin were studied in 126 outpatients suffering from primary unipolar depression ([redacted]). Patients were treated with doses of 1.0-4.5 mg of alprazolam and 50-225 mg of doxepin per day. The mean total Hamilton Psychiatric Rating Scale for Depression (HAM-D) score decreased in each treatment group by 56% over the course of the study. The mean final doses were 2.7 mg for alprazolam and 137.5 mg for doxepin. The mean total Hamilton Anxiety Scale (HAM-A) scores were approximately equal for the two groups throughout the study, decreasing 49% by the end of Week 6. The results indicate that alprazolam and doxepin were equally efficacious. The incidence of side effects was lower in the alprazolam treatment group.

Doxepin was compared to the combination of amitriptyline-perphenazine in a double-blind controlled study conducted with 100 clinic, general practice, and private psychiatric practice outpatients diagnosed as suffering from a mixed anxiety-depressive reaction ([redacted]). The relatively few statistically significant

differences found in the study indicated amitriptyline-perphenazine to be more effective than doxepin (main drug effects), general practice patients to improve the most and private psychiatric patients the least (main population effects), and clinic patients to respond better to doxepin, while general practice and private psychiatric patients improved most with the drug combination (drug) < population interaction effects). Amitriptyline-perphenazine was found to produce more improvement in high and doxepin in low depressed patients, and doxepin was observed to be more effective in lower than in higher social class patients. Patients on doxepin tended to report more side effects, but to drop out less frequently than patients on the drug combination.

MODULE 2 OVERALL SUMMARIES

2.5 Clinical Overview

2.5.5 Overview of Safety

2.5.5.1 Adverse Events Characteristic of Pharmacological Class

Antidepressant drugs are effective and generally well tolerated, but noncompliance remains worrisome ([redacted]). Up to 70% of patients taking antidepressants are noncompliant, as a result of either missed doses or premature discontinuation. About 28% of patients stopped taking antidepressants in the first month of treatment, and 44% discontinued by the third month ([redacted]). Several reasons were identified for premature discontinuation, with side effects the most common. Dropout rates in studies of tricyclic antidepressants varied from 7% to 44%; in studies of serotonin reuptake inhibitors, the dropout rates were 7% to 23%. Benign and transient side effects are more common than dangerous or irreversible effects, especially with the newer antidepressants.

Tricyclic antidepressants block reuptake of norepinephrine and serotonin. They are also competitive antagonists at the muscarinic, histaminergic, and α-1 and α-2 adrenergic receptors, which results in their characteristic side effect profile ([redacted]). Amitriptyline, imipramine, and doxepin have the most anticholinergic activity, whereas nortriptyline and desipramine are less anticholinergic. Anticholinergic side effects include dry mouth, constipation, urinary retention, blurred vision, confusion, and delirium. Narrow-angle glaucoma can be aggravated. Cardiac effects. Tricyclic antidepressants may slow cardiac conduction, causing intraventricular conduction delay, atrioventricular block, flattened T waves, depressed ST segments, and prolonged QT intervals ([redacted]). All tricyclic antidepressants can cause tachycardia, which is one of the most common reasons for stopping them. Nortriptyline is the least likely to cause orthostatic hypotension. Because of cardiotoxicity, an overdose of as little as 1 week's worth of medication can be fatal. Sedation is the most common side effect of tricyclic antidepressants and is a result of anticholinergic and antihistaminergic effects ([redacted]). Doxepin has the highest antihistaminergic activity among tricyclic antidepressants. Weight gain and sexual side effects are also common. A discontinuation syndrome is mostly related to cholinergic and serotonergic rebound. After prolonged treatment, tricyclic antidepressants should be tapered gradually over several weeks. Drug interactions are significant. Serotonin reuptake inhibitors may raise the plasma levels of tricyclic antidepressants. There is a possibility that phenytoin levels increase with tricyclic coadministration. Valproic acid can increase levels of tricyclics, and carbamazepine may decrease those ([redacted]).

2.5.5.2 Adverse events of doxepin

Based on the results of published and unpublished therapeutic trials doxepin is well tolerated; including in the elderly and patients with cardiovascular disease ([redacted]). Although many patients experience side effects, most are mild and generally disappear with continued treatment, or if necessary, by reduction of dosage. Dry mouth, drowsiness or sedation, and constipation are the most common side effects, but are often mild. Excessive daytime drowsiness can generally be avoided by giving the major portion or the total daily dose at bedtime. The incidence of drowsiness does not seem to be related to the severity of the illness at the onset of treatment. Incidence of side effects analysed in two reviews ([redacted]; [redacted]) is shown in Table 6.

Table 6 Incidence of side effects analysed in two reviews

Side effects	All patients (%) ([redacted]) N = 1706	All patients (%) ([redacted]) N = 1183[c]	Depressed patients[a] (%) ([redacted]) N = 917	Anxious patients[b] (%) ([redacted]) N = 266
Drowsiness	17.4	29.1	28.5	31.2
Dry mouth	14.5	27.0	29.1	19.5
Constipation	4.4	9.4	10.3	6.4
Dizziness	5.9	8.7	7.5	12.8
Extrapyramidal reactions	6.3	4.1	3.6	5.6
Blurred vision	3.0	3.8	3.8	3.8
Sweating	2.7	3.8	3.2	1.9
Hypotension	2.8	2.4	3.0	0
Tachycardia	2.6	1.7	1.6	1.9

[a] Includes those with some anxiety component .

[b] Includes those with some depression component.

[c] 1210 for drowsiness; 944 in depressed patients. Some studies recorded other side effects but only gave data for drowsiness.

Less commonly reported side effects include extrapyramidal symptoms (usually mild and consisting of tremor, but sometimes akathisia or gait disturbance), blurred vision, postural hypotension, sweating and tachycardia. Urinary retention has been rare. Some investigators have reported instances of paraesthesia ([redacted]), notable weight gain ([redacted]), excitement ([redacted]), and leukopenia and thrombocytopenia ([redacted]). These and other infrequent side effects are to be expected from tricyclic antidepressants. Liver function abnormalities have been noted

by a number of investigators ([redacted]), but do not seem to be of any clinical significance. Euphoria has been virtually absent and there have been no reports of physical dependence or withdrawal symptoms associated with doxepin therapy. Tricyclic antidepressants have not been associated with drug dependence problems. In general, side effects tended to be dose-related ([redacted]). Drowsiness and tachycardia in particular appear to be dose related. Drowsiness occurred in 7% of patients at doses below 200 mg and in 29% at doses above 200 mg. Headache also seems to be a function of dosage ([redacted]).

2.5.5.3 Effects in Population Sub – Groups

2.5.5.3.1 Pregnancy

Doxepin crosses the placenta. Reproduction studies have been performed in rats, rabbits and monkeys and there was no evidence of harm to the animal foetus. The relevance to humans is not known. Since there is insufficient experience in pregnant women who have received this drug, its safety in pregnancy has not been established. The American College of Obstetricians and Gynecologists (ACOG) recommends that therapy for depression during pregnancy be individualized; treatment should incorporate the clinical expertise of the mental health clinician, obstetrician, primary health care provider, and paediatrician ([redacted]).

2.5.5.3.2 Lactation

Doxepin and its active metabolite DMD are excreted in breast milk. There has been a report of apnoea and drowsiness occurring in a nursing infant whose mother was taking doxepin. The use of doxepin is contraindicated during lactation.

2.5.5.3.3 Paediatric

The use of doxepin in children under 12 years is not recommended because safe conditions for its use have not been established. There is a case report of a five-year-old Hispanic girl developed a generalized eczematous rash for which she was prescribed doxepin hydrochloride 5% cream ([redacted]).

2.5.5.3.4 Elderly

Clinical trials have included patients over 65 years and no adverse reactions specific to this age group have been reported. Elderly patients generally should be started on low doses of doxepin and observed closely. Doses > 6 mg/day should be avoided ([redacted]).

In a randomized, double-blind, placebo-controlled outpatient trial, elderly adults meeting DSM-IV-TR criteria for primary insomnia were randomized to four weeks of nightly treatment with either doxepin 6 mg (n = 130) or placebo (PBO; n = 124)

([redacted]). There were no reports of anticholinergic effects (e.g., dry mouth) or memory impairment. The safety profile of doxepin 6 mg was comparable to that of placebo.

2.5.5.3.4 Gender

Clinical trials have included male and female subjects and no specific gender related adverse reactions have been reported.

2.5.5.3.5 Race

No specific race related adverse reactions have been reported.

2.5.5.4 Overview of Adverse Events of doxepin

AEs have been ranked under headings of frequency using the following convention: very common (≥1/10); common (≥1/100; <1/10); uncommon (≥1/1,000; <1/100); rare (≥1/10,000; <1/1,000); very rare (<1/10,000); frequency not known (cannot be estimated from the available data) (Table 7) ([redacted]).

Table 7 Adverse events of doxepin by system organ class

System organ class	Untoward effect	Frequency
Blood and Lymphatic System Disorders	anemia	uncommon
	thrombocythemia	rare
Cardiac Disorders	atrioventricular block, palpitations, tachycardia, ventricular extrasystoles.	rare
Ear and Labyrinth Disorders	ear pain, hypoacusis, motion sickness, tinnitus, tympanic membrane perforation	rare
Eye Disorders	eye redness, vision blurred	uncommon
	blepharospasm, diplopia, eye pain, lacrimation decreased	rare
Gastrointestinal Disorders	abdominal pain, dry mouth, gastroesophageal reflux disease, vomiting	uncommon
	dyspepsia, constipation, gingival recession, haematochezia, lip blister	rare
General Disorders	asthenia, chest pain, fatigue	uncommon
	chills, gait abnormal, edema peripheral	rare
Hepatobiliary Disorders	hyperbilirubinemia.	rare

Immune System Disorders	hypersensitivity.	rare
Infections and Infestations	bronchitis, fungal infection, laryngitis, sinusitis, tooth infection, urinary tract infection, viral infection	uncommon
	cellulitis staphylococcal, eye infection, folliculitis, gastroenteritis viral, herpes zoster, infective tenosynovitis, influenza, lower respiratory tract infection, onychomycosis, pharyngitis, pneumonia	rare
Investigations	blood glucose increased; Rare: alanine aminotransferase increased, blood pressure decreased, blood pressure increased, electrocardiogram ST-T segment abnormal, electrocardiogram QRS complex abnormal, heart rate decreased, neutrophil count decreased, QRS axis abnormal, transaminases increased	rare
Metabolism and Nutrition Disorders	anorexia, decreased appetite, hyperkalemia, hypermagnesemia, increased appetite	uncommon
	hypokalemia	rare
Musculoskeletal and Connective Tissue Disorders	arthralgia, back pain, myalgia, neck pain, pain in extremity;	uncommon
	joint range of motion decreased, muscle cramp, sensation of heaviness	rare
Neoplasms Benign, Malignant and Unspecified	lung adenocarcinoma stage I, malignant melanoma.	rare
Nervous System Disorders	dizziness;	common
	dysgeusia, lethargy, parasthesia, syncope	uncommon
	ageusia, ataxia, cerebrovascular accident, disturbance in attention, migraine, sleep paralysis, syncope vasovagal, tremor	rare
Psychiatric Disorders	abnormal dreams, adjustment disorder, anxiety, depression	uncommon
	confusional state, elevated mood, insomnia, libido decreased, nightmare	rare

Reproductive System and Breast Disorders	breast cyst, dysmenorrhea	rare
Renal and Urinary Disorders	dysuria, enuresis, hemoglobinuria, nocturia	rare
Respiratory, Thoracic and Mediastinal Disorders	nasal congestion, pharyngolaryngeal pain, sinus congestion, wheezing	uncommon
	cough, crackles lung, nasopharyngeal disorder, rhinorrhea, dyspnea.	rare
Skin and Subcutaneous Tissue Disorders	skin irritation	uncommon
	sweat, dermatitis, erythema, hyperhidrosis, pruritis, rash, rosacea	rare
Vascular Disorders	pallor	uncommon
	blood pressure inadequately controlled, hematoma, hot flush	rare

2.5.5.5 Overdose

2.5.5.5.1 Experience and Symptoms

Deaths may occur from overdosage with this class of drugs ([redacted]). Multiple drug ingestion (including alcohol) is common in deliberate tricyclic antidepressant overdose. As the management is complex and changing, it is recommended that the physician contact a poison control center for current information on treatment. Signs and symptoms of toxicity develop rapidly after tricyclic antidepressant overdose; therefore, hospital monitoring is required as soon as possible.

Critical manifestations of overdose include: cardiac dysrhythmias, severe hypotension, convulsions and CNS depression, including coma. Changes in the electrocardiogram, particularly in QRS axis or width, are clinically significant indicators of tricyclic antidepressant toxicity. Other signs of overdose may include: confusion, disturbed concentration, transient visual hallucinations, dilated pupils, agitation, hyperactive reflexes, stupor, drowsiness, muscle rigidity, vomiting, hypothermia, and hyperpyrexia.

2.5.5.5.2 Treatment

General

Obtain an ECG and immediately initiate cardiac monitoring. Protect the patient's airway, establish an intravenous line and initiate gastric decontamination ([redacted]). A minimum of 6 hours of observation with

cardiac monitoring and observation for signs of CNS or respiratory depression, hypotension, cardiac dysrhythmias and/or conduction blocks, and seizures is strongly advised. If signs of toxicity occur at any time during this period, extended monitoring is recommended. There are case reports of patients succumbing to fatal dysrhythmias late after overdose; these patients had clinical evidence of significant poisoning prior to death and most received inadequate GI decontamination. Monitoring of plasma drug levels should not guide management of the patient.

Gastrointestinal Decontamination

All patients suspected of tricyclic antidepressant overdose should receive GI decontamination. This should include large volume gastric lavage followed by activated charcoal. If consciousness is impaired, the airway should be secured prior to lavage. Emesis is contraindicated.

Cardiovascular

A maximal limb lead QRS duration of $\geq$ 0.10 seconds may be the best indication of the severity of the overdose. Intravenous sodium bicarbonate should be used to maintain the serum pH in the range of 7.45 to 7.55. If the pH response is inadequate, hyperventilation may also be used. Concomitant use of hyperventilation and sodium bicarbonate should be done with extreme caution, with frequent pH monitoring. A pH > 7.60 or a pCO < 20 mm Hg is undesirable. Dysrhythmias unresponsive to sodium bicarbonate therapy/hyperventilation may respond to lidocaine, bretylium or phenytoin. Type 1A and 1C antiarrhythmics are generally contraindicated (e.g., quinidine, disopyramide and procainamide). In rare instances, haemoperfusion may be beneficial in acute refractory cardiovascular instability in patients with acute toxicity. However, haemodialysis, peritoneal dialysis, exchange transfusions and forced diuresis generally have been reported as ineffective in tricyclic antidepressant poisoning.

CNS

In patients with CNS depression, early intubation is advised because of the potential for abrupt deterioration. Seizures should be controlled with benzodiazepines, or if these are ineffective, other anticonvulsants (e.g., phenobarbital, phenytoin). Physostigmine is not recommended except to treat life-threatening symptoms that have been unresponsive to other therapies, and then only in consultation with a poison control centre.

Psychiatric Follow-up

Since overdosage is often deliberate, patients may attempt suicide by other means during the recovery phase. Psychiatric referral may be appropriate.

Paediatric Management

The principles of management of child and adult overdosages are similar. It is strongly recommended that the physician contact the local poison control centre for specific paediatric treatment.

2.5.5.6 World Wide Marketing Experience

Postmarketing, and/or case reports include the following AEs, the frequency of each is <1% ([redacted]). Abdominal pain, abnormal dreams, abnormal gait, acne rosacea, adenocarcinoma (lung, stage I), adjustment disorder, ageusia, altered blood pressure (inadequately controlled), anemia, angle-closure glaucoma, anxiety, arthralgia, atrioventricular block, back injury, back pain, blepharospasm, bone fracture, breast cyst, bronchitis, cerebrovascular accident, change in appetite, chest pain, confusion, cough, decreased heart rate, decreased lacrimation, decreased neutrophils, decreased performance on neuropsychometrics, decreased range of motion (joints), depression, dermatitis, diplopia, disturbance in attention, dysmenorrhea, dyspnea, dysuria, ECG abnormality (ST-T segment, QRS complex, QRS axis), erythema, eye infection, eye pain, eye redness, falling, feeling of heaviness, folliculitis, fungal infection, gastroesophageal reflux disease, gum line erosion, hematochezia, hematoma, hemoglobinuria, herpes zoster, hot flash, hyperbilirubinemia, hyperhidrosis, hyperkalemia, hypermagnesemia, hypersenitivity, hypoacusis, hypokalemia, increased serum ALT, increased serum transaminases, influenza, joint sprain, laceration, laryngitis, lethargy, limb pain, lip blister, lower respiratory tract infection, malignant melanoma, migraine, mood elevation, motion sickness, muscle cramps, myalgia, nasal congestion, nasopharyngeal disorder, neck pain, nightmares, nocturia, onychomycosis, otalgia, pallor, palpitations, perforated tympanic membrane peripheral edema, haryngitis, pharyngolaryngeal pain, pneumonia, rales, rhinorrhea, sinus congestion, sinusitis, skin irritation, sleep paralysis, somnambulism (complex sleep-related behavior [sleep-driving, cooking or eating food, making phone calls]), staphylococcal cellulitis, syncope, tenosynovitis, tooth infection, urinary incontinence, urinary tract infection, vasodepressor syncope, ventricular premature contractions, viral infection, wheezing

MODULE 2 OVERALL SUMMARIES

2.5 Clinical Overview

2.5.6 Benefits and Risks Conclusions

This Clinical Overview of the medicinal product candidates Doxepin 10 mg, 25 mg and 50 mg Capsules of Morningside Healthcare Ltd, UK has been compiled for evaluating literary data about the clinical efficacy and safety properties of doxepin in preparation of Applications for Marketing Authorisation of Doxepin 25 mg and 50 mg Capsules of Morningside Healthcare Ltd, UK according to EU Directive 2001/83/EC Article 10(1) and that of Doxepin 10 mg Capsule of Morningside Healthcare Ltd, UK according to EU Directive 2001/83/EC Article 10(3).

2.5.6.1. Global Assessment of Efficacy

Doxepin is a potent antihistamine of the tricyclic antidepressants, with four times the potency of amitriptyline and 800 times the potency of diphenhydramine at the H_1 receptor. At standard antidepressant doses (> 75 mg/day), doxepin inhibits the reuptake of serotonin and norepinephrine and antagonizes cholinergic, histaminergic, and α-adrenergic activity.

Findings of randomized controlled trials have confirmed the significant superiority of doxepin over a placebo. Active-controlled trials suggest that doxepin has a profile of activity similar to that of amitriptyline. In comparison with amitriptyline or imipramine, doxepin has been demonstrated clinically equally effective, but in most cases with fewer or less troublesome side effects. Improvement in disturbed sleep pattern seems to be better than that achieved with imipramine and comparable with that attained by amitriptyline. A single bedtime dose appears to be more desirable than a divided daily dose regimen in most patients. Doxepin has a significant effect on symptoms of insomnia and anxiety with a significant but slightly lesser effect on agitation, depressed mood, psychomotor retardation, guilt, and suicidal ideation.

Patients with endogenous depression tend to respond as well or better than those with reactive or involutional depression. In most studies, a minimum dosage of 75mg daily was needed to achieve improvement; with the most effective daily dosage ranging from 100/150 to 200/300mg daily. Patients with psychotic depression have required larger doses than those with neurotic depression. Although a few patients begin to improve during the first week of therapy on a divided dose regimen, the antidepressant effect in most patients generally occurs after 7 to 10 or more days. The earlier a beneficial effect occurred, the better the eventual outcome. Doxepin has been used effectively as maintenance therapy for periods of up to 4 to 7 years in patients with manic-depressive psychosis (depressive phase) and has been well tolerated. Five weeks of nightly

administration of doxepin 3 mg and 6 mg to adults with chronic primary insomnia resulted in significant and sustained improvements in sleep maintenance and early morning awakenings. These sleep improvements were not accompanied by next-day residual effects or followed by rebound insomnia or withdrawal effects upon discontinuation.

Due to its multiple pharmacodynamics activities, doxepin has been tried for the treatment of oral mucositis–related pain, itching, urticaria, pain, insomnia, autonomic system dysfunction, IBR, ulcer, etc. These are briefly discussed under the section of Secondary Pharmacodynamics, although these therapeutic effects cannot be sharply segregated from the primary pharmacodynamic actions.

Low-dose doxepin has a terminal half-life of 15.3 hours, whereas T_{max} occurs between 1.3 and 3.5 hours after oral administration to healthy fasted subjects. T_{max} is delayed by approximately 3 hours if the drug is taken with a high-fat meal, and AUC is increased by 41% and C_{max} by 15%. For this reason, it is recommended that doxepin be taken without food, to minimize the risk of next day effects. The major liver enzymes responsible for the metabolism of doxepin are CYP2C19 and CYP2D6, while CYP1A2 and CYP2C9 are involved to a lesser extent. CYP 2C19 is a key enzyme for N-methylation of doxepin and 2C9 and 1A2 plays a role as well in N-demethylation but to a lesser extent. CYP 2D6 is a key enzyme involved in the hydroxylation of doxepin. The drug is about 85% bound to plasma proteins.

2.5.6.2. Global Assessment of Safety

Numerous controlled comparative trials have been conducted in hospitalised inpatients. Trial results listed in the overview demonstrate that doxepin is well tolerated. Although many patients experience side effects, they are mostly mild and generally disappear with continued treatment, or if necessary, by reduction of dosage. Even elderly patients and those with cardiovascular disease demonstrate reasonable tolerance. The frequency of most of the AEs is either uncommon or rare. Anticholinergic effects include dry mouth, blurred vision, constipation and urinary retention. The most commonly noticed CNS side effect is drowsiness. Other infrequently reported CNS AEs are confusion, disorientation, hallucinations, numbness, paraesthesia, ataxia, extrapyramidal symptoms, seizures, tardive dyskinesia and tremor. Cardiovascular effects include hypotension, hypertension and tachycardia. Allergic reactions include skin rash, oedema, photosensitization and pruritus. Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia and purpura. Gastrointestinal AEs include nausea, vomiting, indigestion, taste disturbances, diarrhoea, anorexia, and aphthous stomatitis. Endocrine AEs are manifested in raised or lowered libido,

testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhoea in the female, raising or lowering of blood sugar levels and syndrome of inappropriate antidiuretic hormone secretion. Additional AEs may be dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, headache, exacerbation of asthma, angle closure glaucoma, mydriasis and hyperpyrexia (in association with chlorpromazine).

2.5.6.3 Overall Conclusion

Doxepin was discovered in Germany in 1963 and was introduced in the US as an antidepressant in 1969. Doxepin-containing drug products are currently available all over the world. Clinical trials and the over fifty-year worldwide experience in human therapy support the claim that doxepin can be used for treatment of symptoms of depressive illness, especially where sedation is required. In clinical practice, the recommended daily oral dose of doxepin may vary from 25-300 mg.

The proposed pharmaceutical formulation of the drug products does not contain any novel excipient, or excipient being administered by a novel route, and, therefore, there is no unexpected toxicological potential.

Although the nature of the cited scientific literature does not allow any comment on the Good Laboratory Practice (GLP) and the Good Clinical Practice (GCP) status, most of the cited experimental studies have been published in peer-reviewed journals; and monographs are published in reference textbooks of clinical pharmacology, and in formularies. These limitations are not considered as critical predominantly because of its over 50-year worldwide history of human clinical use.

The bioequivalence study conducted by the Applicant was performed in full accordance, as applicable, with current standards of Good Manufacturing Practice (GMP), GCP, and GLP, complied with these standards, was in accordance with the Declaration of Helsinki, and was subject to independent Ethics Committee review.

The benefits of doxepin and its place for the management treatment of symptoms of depressive illness, especially where sedation is required have been established in the several decades of clinical usage within the EU and in many other countries all over the world. Practical experience with doxepin on the market in a large number of patients has also confirmed its safety and efficacy when used as directed.

The Summary of Product Characteristics (SmPC) proposed by the Applicant takes the available pharmacodynamic, pharmacokinetic, toxicological, and clinical evidence into account, and is in accordance with the current knowledge in respect of the active moiety.

Doxepin 50 mg Capsules of Morningside Healthcare Ltd, UK contain the same active substance, doxepin, in a similar formulation with respect to the cited Reference Products, Doxepin Hydrochloride BP 50 mg capsules of Marlborough Pharmaceuticals Ltd., UK; and therapeutic equivalence has been demonstrated in full accordance with all applicable current guidance.

In conclusion, doxepin-containing medications have been marketed for over 50 years in countries belonging to the EU since 1993. The drug candidates Doxepin 10 mg, 25 mg and 50 mg Capsules of Morningside Healthcare Ltd, UK meet the requirements of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

MODULE 2 OVERALL SUMMARIES

2.5 Clinical Overview

2.5.7 Cited Literature References

Module	#	References
5	1.	[redacted]
5	2.	[redacted]
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