International Journal of Pharmaceutics 393 (2010) 55–60

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Rapidfilm®: An innovative pharmaceutical form designed to improve patient compliance

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ARTICLE INFO

Article history:
Received 13 January 2010
Received in revised form 22 March 2010
Accepted 27 March 2010
Available online 2 April 2010

Keywords:
Ondansetron
Orally disintegrating tablet (ODT)
Orodispersible tablet
Bioequivalence
Orodispersible film
Delivery system

ABSTRACT

The aim of the research was to assess the bioequivalence between Rapidfilm®, a new patented delivery system, versus the traditional orodispersible tablet (ODT).

A randomized, two-way, single dose, crossover, bioequivalence study was conducted in 24 fasting, healthy volunteers with two formulations of ondansetron (Ondansetron Rapidfilm® vs. Zofran® Zydis® Lingual ODT by GlaxoSmithKline GmbH & Co. KG).

Plasma samples were analysed by a validated LC–MS/MS method during a collection period of 24 h post-dosing. The analysis of variance (ANOVA) on the targeted pharmacokinetic parameters did not show any significant difference between the two formulations and 90% confidence intervals (CIs) fell within the common acceptance range of 80–125%, satisfying the bioequivalence criteria. These results allow Rapidfilm® to claim the same panel of indications of the conventional immediate release oral solid dosage forms, but offering several advantages also over the ODT: it can result in higher patient convenience for several applications.

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1. Introduction

Ondansetron is an inhibitor of 5-HT^3 receptors used orally, intravenously, intramuscularly or rectally for the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy, the prevention of postoperative nausea and vomiting (POVN) and the prevention of radiation-induced nausea and vomiting.

Ondansetron is available as hydrochloride dihydrate salt in tablets, while it is included as base in orodispersible tablets (ODTs). Regular ondansetron tablets (Zofran®, GlaxoSmithKline) and ondansetron ODT (Zofran® ODT or Zofran® Zydis®) have been shown to be bioequivalent.

Ondansetron Rapidfilm® is an orodispersible pharmaceutical form complying with the orodispersible tablet definition of the European Pharmacopoeia, but instead of compressing, it is obtained by casting a polymer mass (Fig. 1, panel A).

Placed on top of the tongue, the film disperses within seconds without water and it is particularly suitable for patients with difficulties in swallowing conventional tablets, for example paediatric patients, elderly people and patients with oral chemotherapy- and/or radiotherapy-induced mucositis (Habib et al., 2000; Biradar et al., 2006). It is available in two different strengths containing 4 and 8 mg of the active drug substance ondansetron base, derived by die cutting of the film from the same laminate, sized 3 and 6 cm^2, respectively.

Considering the target population, the Ondansetron Rapidfilm® was especially designed for higher patient compliance. Patients on chemotherapy treatment may have intense nausea that makes difficult the administration of conventional tablets with water, especially those with head and neck or oesophageal cancers.

Ondansetron Rapidfilm® offers multiple competitive advantages versus the already marketed oral pharmaceutical forms of ondansetron:

- versus tablets: swallowing is easier and water unnecessary,
- versus syrup: no liquid intake and strawberry taste in the mouth, easier dosing accuracy, shorter handling time, and
- versus ODT: easier to be handled, stored and taken away.

In addition, the absence of aspartame in the formulation makes it safe also for phenylketonuric patients who are contraindicated to the use of Zofran® Zydis®, the ondansetron orodispersible tablets by GlaxoSmithKline GmbH & Co.

This paper compares the bioavailability of Ondansetron Rapidfilm® 8 mg to that of ondansetron orodispersible tablet (ODT) 8 mg (Zofran® Zydis®) with the aim of demonstrating the bioequivalence of the formulations, allowing to claim the same panel of

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doi:10.1016/j.ijpharm.2010.03.055

Fig. 1. Panel A: sample of Ondansetron Rapidfilm®. Panel B: packaging of Ondansetron Rapidfilm®, with the labelling of the clinical study.

indications (Davidson et al., 1999; LeBourgeois et al., 1999; Gan et al., 2002; Cohen et al., 2005; Wagner et al., 2007).

2. Materials and methods

2.1. Study investigational medicinal products

Ondansetron Rapidfilm® uses the Rapidfilm® drug delivery technology, developed in joint venture by APR Applied Pharma Research SA and Labtec GmbH, a company belonging to the group of tesa. It is a novel oral delivery system: fast-dissolving film strip. Ondansetron Rapidfilm® 8 mg, orodispersible films, batch no. 7039637, was released for clinical trial by Labtec GmbH. Zofran® 8 mg Zydis® Lingual, ODT (orodispersible tablet), batch no. 6M001, manufactured by GlaxoSmithKline GmbH & Co, was bought in a German pharmacy.

2.2. Study design

This study was performed at Scope Life Sciences GmbH (CRO in Hamburg) according to the rules of Good Clinical Practice. The protocol of this study was approved by 'Ethik-Kommission der Ärztekammer Hamburg'; the clinical trial application was provided to the German Authority (BfArM); the trial was notified to the local Hamburg authority in accordance with § 67 Abs. 1 AMG.

The study was carried out according to an open, randomized, two-period, crossover (with a 1-week washout period) design. Subjects were admitted into hospital at 7:00 p.m. the day before the study and fasted 12 h before each drug administration. A single dose (8 mg) consisting of one Ondansetron Rapidfilm® or Zofran® Zydis® ODT according to the randomization plan was given to each subject in a fasting state for each treatment period. Fasting continued for a further 4 h after drug administration. The drug was administered without water. Subjects drank 150 ml of mineral water at room temperature 1 h before administration; then, water was forbidden until 2 h after dosing. Subjects were provided with standard meals 4 h (lunch), 7 h (snack) and 11 h (supper) post-dosing.

A total of 24 Caucasian healthy volunteers, 12 females and 12 males, participated in the study after signing a consent form. Subjects were mean age of 39 years, had mean body weight of 72.7 kg, and mean height of 1.76 m. Subjects with clinically significant abnormalities/disorders, history of drug allergies, alcohol and drug abuse were not enrolled. Subjects were selected after a clinical screening procedure including a physical examination and laboratory tests. All subjects avoided using other drugs for at least 2 weeks prior to the study and until after its completion. They also abstained from drinking coffee, tea, cocoa, cola, citrus/grape fruit, citrus/grape juice and alcohol beverages, from 36 h prior to each dosing and until the collection of the last blood sample. During the hospitalisation, consumption of tobacco was not allowed. The consumption of food containing poppy seeds (muffins, bagels and cakes) was forbidden from 7 days prior to the first dosing until the last sampling.

2.3. Sample collection

Blood samples, 9 ml each, were collected directly from a vein into EDTA-coated tubes, according to the time schedule, which included a blank sample just prior to dosing and then at 00:15; 00:30; 00:45; 01:00; 01:15; 01:30; 01:45; 02:00; 02:30; 03:00; 03:30; 04:00; 06:00; 08:00; 10:00; 12:00, 16:00; 24:00 h after drug administration.

Any deviation from the stated sampling times was recorded. Plasma was immediately separated by centrifugation at $2750 \times g$ for 10 min and 4 °C, then was transferred to properly labelled tubes and stored at −20 °C until the LC–MS/MS assay.

2.4. Bioanalytical method

All bioanalytical work was done according to Good Laboratory Practice (GLP) at Scope Life Sciences GmbH.

All plasma samples were analysed for ondansetron concentration according to a sensitive, selective, accurate and validated LC–MS/MS method. Calibration standards and quality control plasma samples were prepared by spiking blank EDTA plasma with standard solutions of ondansetron. The specificity of the method for interference of endogenous compounds was investigated by testing 10 individual sources of blank matrix without addition of internal standard.

The linearity was evaluated using $1/x$ linear regression analysis in the range 0.2–100 ng/ml.

The lower limit of quantification (LLOQ = 0.2 ng/ml) was defined as the lowest ondansetron concentration of the calibration curve which could be determined with an intra-assay precision <20%. The recovery was calculated by comparing the peak areas of extracted plasma standards at the three quality control concentration levels ($n = 6$) to the mean from those of standard solution mixtures at the same concentration ($n = 6$).

Inter- and intra-assay precision and accuracy were determined by repeated analysis of quality control plasma samples (LLOQ, 0.56, 40 and 80 ng/ml) on the same day and on different days. Stability of ondansetron was determined in spiked quality control samples at room temperature (2, 4 and 24 h standing) and through three freeze–thaw cycles. The samples were analysed sixfold.

2.5. Pharmacokinetics and statistical analyses

The following pharmacokinetic parameters were calculated using non-compartmental methods: area under the plasma concentration–time curve from zero to the last measurable

ondansetron concentration sample time (AUC_{0-t}), area under the plasma concentration–time curve extrapolated to infinite time ($AUC_{0-\infty}$), maximum plasma drug concentration (C_{max}) and time to reach C_{max} (t_{max}), C_{max}/AUC_{0-t}, t_{lag} and apparent terminal half-life ($t_{1/2}$). C_{max} and t_{max} were obtained directly from the concentration–time curve. AUC_{0-t} was calculated using the linear trapezoidal method. Elimination rate constant Kel was calculated by applying a log-linear regression from the linear portion of the logarithmic transformed concentration–time plot. The algorithm started with the last three points with concentration >LLOQ.

$t_{1/2}$ was calculated as 0.693/Kel. $AUC_{0-\infty}$ was calculated summing AUC_{0-t} and the last extrapolated part of the curve obtained by C_{last}/Kel. t_{lag} was the delay between the time of administration and the time of the first detectable plasma concentration.

For the purpose of bioequivalence analysis AUC_{0-t} and C_{max} were considered as primary variables.

Analysis of variance (ANOVA) was applied to the log-transformed pharmacokinetic parameters considered primary variables. The effects considered in the ANOVA model were treatment, sequence, study period, and subject within sequence.

Bioequivalence between the products was determined by calculating 90% confidence intervals (90% CIs) for the ratio of geometric means of C_{max} and AUC_{0-t} values for the test and reference products.

The products were considered bioequivalent if the 90% CIs for AUC_{0-t} and C_{max} fell within 80–125%.

For t_{max}, $t_{1/2}$ and t_{lag} the non-parametric point estimator and the non-parametric 90% confidence intervals for the difference of expected medians were calculated according to Mann–Whitney/Wilcoxon, using the untransformed data.

The gender effect was evaluated. Descriptive statistics were calculated for each gender group (12 subjects each). A second ANOVA model was used with sequence, sex, study period, treatment and treatment by sex interaction as fixed effects.

3. Results

3.1. Safety

The overall incidence of adverse events was evenly distributed across all treatment groups, and no serious adverse events were reported. Generally, both study medications were well tolerated.

Ten adverse events (AEs) were reported by 9 out of the 24 subjects treated: 3 AEs by 3 (13%) of 24 subjects during treatment with Ondansetron Rapidfilm®; 7 AEs by 7 (29%) of 24 subjects during treatment Zofran® Zydis® ODT. The reported AEs were headache and dizziness, constipation, haematochezia, oral herpes and blurred vision. All AEs resolved completely. There was no drop-out. No relevant changes in clinical laboratory variables, vital signs, ECG parameters or in physical findings were detected at the end of the study.

3.2. Pharmacokinetic results

The plasma drug concentration–time curves show that the mean concentrations of ondansetron were superimposable for the two formulations over the 24-h sampling period (Fig. 2).

Descriptive statistics (arithmetic and geometric mean, standard deviation, minimum and maximum, median) for the investigated pharmacokinetic variables are reported in Table 1. The results after statistical analysis of the main pharmacokinetic parameters are shown in Table 2. The 90% confidence intervals of geometric mean and point estimator of the AUC_{0-t} ratio (95.19% [87.49–103.58%]) and the $AUC_{0-\infty}$ ratio (93.34% [85.01–102.49%]) as well as the

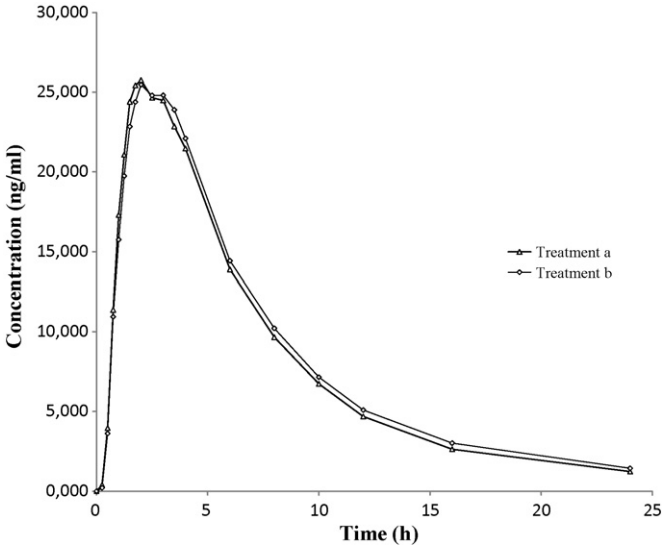

Fig. 2. Ondansetron plasma mean concentrations versus time profile obtained after single oral administration of Ondansetron 8 mg Rapidfilm® (a) vs. Zofran® Zydis® 8 mg ODT (b).

C_{max} ratio (98.27% [91.33–105.74%]) are included by the common acceptance range for bioequivalence (80–125%). The same is true for the 90% confidence interval of C_{max}/AUC_{0-t} ratio 103.23% [97.11–109.74%].

The intra-subject variability in terms of the ANOVA-CV of 17.2% for AUC_{0-t} was slightly higher than anticipated for the sample size estimation (<12%). The variability of C_{max} (14.9%), in contrast, was lower than anticipated (<20%). The 90% confidence intervals therefore could be estimated with an adequate precision. Taking the point estimators and the ANOVA-CVs determined in the study, the retrospective power of the study to demonstrate bioequivalence (acceptance range 80–125%) with respect to AUC_{0-t} and C_{max} exceeded 95%.

A gender effect was observed for both the rate and extent of absorption without differences between formulations (Table 3). Starting from the geometric means, the $AUC_{0-\infty}$ female/$AUC_{0-\infty}$ male ratios are 1.32 for test and 1.15 for reference; values of 1.23 and 1.11, respectively were calculated for C_{max}. No differences are observed for the terminal elimination half-life. The ANOVA according to the second model showed no significant differences between gender groups ($p > 0.05$).

4. Discussion

No serious or unexpected adverse events were reported or observed during the study. The drug formulations were well tolerated by all subjects.

The bioequivalence of Ondansetron Rapidfilm® 8 mg test formulation compared to the reference formulation was demonstrated. 90% CIs of AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} ratios of ondansetron of these two preparations fell within the 80–125% interval proposed by the guidelines. Both formulations were equivalent in terms of rate and extent of absorption. Consequently, bioequivalence between the two formulations can be concluded. These results suggest that the Rapidfilm® pharmaceutical form promotes a gastrointestinal absorption comparable to immediate release oral solid dosage forms.

Ondansetron Rapidfilm® did not modify the intrinsic gender effect observed with all formulations of ondansetron, including ondansetron ODT. Taking into consideration that no change has been detected with respect to the terminal elimination half-life,

Table 1
Selected descriptive statistics for the investigated pharmacokinetic variables.

Variable	Statistics	*a*	*b*
$AUC_{0-\infty}$ [ng/ml h]	*N*	24	24
	Mean	202.7	214.2
	SD	88.9	86.2
	GeoM	182.9	195.9
	G_CV	51.2	47.5
AUC_{0-t} [ng/ml h]	*N*	24	24
	Mean	193.9	201.3
	SD	82.4	79.1
	GeoM	176.0	184.9
	G_CV	49.5	46.2
C_{max} [ng/ml]	*N*	24	24
	Mean	28.378	28.650
	SD	9.933	9.249
	GeoM	26.602	27.070
	G_CV	39.6	37.4
C_{max}/AUC_{0-t} [1/h]	*N*	24	24
	Mean	0.153	0.151
	SD	0.027	0.037
	GeoM	0.151	0.146
	G_CV	17.5	24.5
r_{AUC} [%]	*N*	24	24
$(1 - AUC_{0-t}/AUC_{0-\infty}) \times 100$	Mean	3.7	5.5
(extrapolated portion of AUC)	SD	2.3	5.4
	Min	1.0	0.7
	Med	3.0	3.7
	Max	10.4	26.9
R (coefficient of correlation)	*N*	24	24
	Mean	−0.993	−0.994
	SD	0.005	0.006
	Min	−1.000	−1.000
	Med	−0.994	−0.997
	Max	−0.980	−0.980
$t_{1/2}$ [h] (half-life)	*N*	24	24
	Mean	5.02	5.79
	SD	1.13	1.94
	GeoM	4.91	5.55
	G_CV	21.9	29.1
t_{lag} [h] (delay between administration and first detectable plasma	*N*	24	24
concentration)	Mean	0.13	0.19
	SD	0.13	0.18
	Min	0.00	0.00
	Med	0.13	0.25
	Max	0.30	0.50
t_{max} [h] (time at which C_{max} occurs)	*N*	24	24
	Mean	2.14	2.31
	SD	0.73	0.86
	Min	1.25	0.75
	Med	1.75	2.00
	Max	4.00	4.00

a: TEST, Ondansetron Rapidfilm®, an orally disintegrating film containing 8 mg ondansetron, *b*: REFERENCE, Zofran® 8 mg Zydis® ODT, an orally disintegrating tablet containing 8 mg ondansetron; *N* = number of subjects, mean = algebraic mean; SD = standard deviation; GeoM = geometric mean; G_CV = coefficient of variation (%) of geometric mean; Min = minimum value; Med = median; Max = maximum value; AUC = area under the concentration time curve; C_{max} = highest concentration determined in the measuring interval.

Table 2
90% Confidence intervals during single dose administration of 8 mg test and reference formulations in 24 healthy subjects.

PKVAR	METHOD	TRANS	COMP	PE	LL	UL	ANOVA-CV
$AUC_{0-\infty}$	ANOVA	Log	*a*/*b*	93.34	85.01	102.49	19.0
AUC_{0-t}	ANOVA	Log	*a*/*b*	95.19	87.49	103.58	17.2
C_{max}	ANOVA	Log	*a*/*b*	98.27	91.33	105.74	14.9
C_{max}/AUC_{0-t}	ANOVA	Log	*a*/*b*	103.23	97.11	109.74	12.4

PKVAR = pharmacokinetic variables; TRANS = transformation; COMP = comparison; PE = point estimator; LL = lower limit; UL = upper limit; ANOVA = analysis of variance; ANOVA-CV = intra-individual coefficient of variation; AUC = area under the concentration time curve; C_{max} = highest concentration determined in the measuring interval.

Table 3
Kinetic variables in subgroups.

Stat.	Variable	Female subjects		Male subjects	
		a	*b*	*a*	*b*
N	$AUC_{0-\infty}$ [ng/ml h]	12	12	12	12
Mean		226.9	227.6	178.5	200.7
SD		90.4	91.1	84.1	82.7
Med		213.7	236.5	173.2	202.2
GeoM		209.9	210.2	159.3	182.7
G_CV		44.4	44.9	55.1	51.1
N	AUC_{0-t} [ng/ml h]	12	12	12	12
Mean		217.3	214.0	170.5	188.6
SD		84.5	79.7	76.4	79.8
Med		205.1	223.2	169.4	196.5
GeoM		201.9	199.6	153.5	171.3
G_CV		43.0	41.6	53.0	51.1
N	C_{max} [ng/ml]	12	12	12	12
Mean		31.072	29.346	25.684	27.953
SD		10.327	6.962	9.155	11.373
Med		28.820	29.158	25.809	27.857
GeoM		29.508	28.541	23.982	25.675
G_CV		34.9	25.7	42.5	47.5
N	C_{max}/AUC_{0-t}	12	12	12	12
Mean		0.147	0.146	0.159	0.156
SD		0.020	0.030	0.032	0.044
Med		0.140	0.135	0.152	0.145
GeoM		0.146	0.143	0.156	0.150
G_CV		13.2	19.7	21.0	29.3
N	λ_z [1/h] (apparent terminal rate constant)	12	12	12	12
Mean		0.140	0.131	0.149	0.128
SD		0.029	0.038	0.032	0.031
Max		0.198	0.212	0.192	0.164
GeoM		0.137	0.127	0.145	0.123
G_CV		20.9	27.3	23.4	32.0
N	$r_{AUC} = 1 - AUC_{0-t}/AUC_{0-\infty}$ (extrapolated portion of AUC)	12	12	12	12
Min		1.0	0.7	1.1	1.6
Med		3.4	4.4	2.6	3.2
Max		7.1	10.1	10.4	26.9
N	*R* (coefficient of correlation)	12	12	12	12
Min		−1.000	−1.000	−1.000	−1.000
Med		−0.995	−1.000	−0.993	−0.994
Max		−0.986	−0.980	−0.980	−0.981
N	$t_{1/2}$ [h] (half-life)	12	12	12	12
Mean		5.15	5.65	4.89	5.92
SD		1.09	1.41	1.20	2.42
Med		5.12	5.73	4.60	5.07
GeoM		5.05	5.48	4.77	5.62
G_CV		20.9	27.3	23.4	32.0
N	t_{lag} [h] (delay between administration and first detectable plasma concentration)	12	12	12	12
Mean		0.13	0.29	0.13	0.08
SD		0.14	0.18	0.13	0.12
Min		0.00	0.00	0.00	0.00
Med		0.13	0.25	0.13	0.00
Max		0.30	0.50	0.25	0.25
N	t_{max} [h] (time at which C_{max} occurs)	12	12	12	12
Mean		2.04	2.27	2.23	2.36
SD		0.60	0.71	0.86	1.02
Min		1.50	1.00	1.25	0.75
Med		1.75	2.00	1.88	2.00
Max		3.00	3.52	4.00	4.00

a: TEST, Ondansetron Rapidfilm®, an orally disintegrating film containing 8 mg ondansetron, *b*: REFERENCE, Zofran® 8 mg Zydis® ODT, an orally disintegrating tablet containing 8 mg ondansetron; *N* = number of subjects, mean = algebraic mean; SD = standard deviation; GeoM = geometric mean; G_CV = coefficient of variation (%) of geometric mean; Min = minimum value; Med = median; Max = maximum value; AUC = area under the concentration time curve; C_{max} = highest concentration determined in the measuring interval.

the different absorption could be explained by a difference in the volume of distribution.

Rapidfilm® is a delivery system offering several advantages over the conventional ODT. Manufacturing is easier and cheaper than that of ODT. ODTs are usually produced by freeze-drying which is a very difficult and cost-consuming procedure. The components of the dosage form are dissolved and special high-priced additives as cryo-protectors are added. The final step is a very energy-consuming freeze-drying procedure. Rapidfilms®, in contrast, are easily produced from a polymer-solution and casting process. The

polymer, API and excipients are dissolved in water and the resulting viscous mixture is casted onto a carrier film. The casting is a continuous process that yields high amounts of film in short time. The resulting wet film is then dried at low temperatures to achieve the bulk intermediate product. Final films are then cut or punched from the intermediate product. Different dosages can be achieved by simply varying the final film size. The effectiveness of this process is thus very high. When compared to Rapidfilm®, the productive capacity of freeze-dryed ODTs is lower and the energy consumption is higher.

From the end-user view, Rapidfilm® is a friendlier user and less fragile form than ODT, allowing easy storage and carry-on during travel. The risk of destroying the dosage form during the removal from its pouch/blister is reduced. ODTs produced by a freeze-drying process are often very porous, brittle and fragile. They may thus be crushed when removed from its primary packaging, leading to uncertain and inadequate dose administered. In contrast, Rapidfilm® is flexible and, to a certain extent, elastic. Stressing the material during removal from the pouch (Fig. 1, panel B) will not result in instant destruction of the dosage form. A proper administration of the film by the patient is secured. The small size and flexibility is also of use for people travelling or having the medication in their carry-on bags (e.g., handbags). The film does not take away much space and can even be carried along in the chest pocket of a shirt. Physical stress of transport (bending, streching, etc.) will not affect the integrity of the dosage form.

Additionally, compared to a Rapidfilm®, ODTs are rather big and bulky. So, the thin film may alleviate the fear of swallowing and the risk of choking commonly associated with a conventional tablet. Furthermore, the fast-dissolving action, primarily due to the wide surface area of the film, which wets quickly when exposed to the moist oral environment, can make Rapidfilm® dissolving in small amounts of liquid: this can be beneficial for people suffering from reduced salivary secretion including chemotherapy- and/or radiotherapy-induced mucositis or sicca syndroma (Sjögren's syndrome).

In conclusion the Rapidfilm® delivery system, by alleviating the administration by the end-user and by allowing patients to take their medication anytime and anyplace under all circumstances, can result in higher convenience for several applications.

Conflict of interest

All the authors are currently employed by APR SA or Labtec GmbH. These companies are the owners of the product. Considering that, at the time of the publication of this article, the product has already been licensed to third parts worldwide, and that its brand name for the market is not mentioned in the article ("Ondansetron Rapidfilm®" was just the name used during the development steps), APR SA and Labtec GmbH do not expect to receive any additional financial benefits from the publication of this paper.

Acknowledgements

We thank all Scope Life Sciences GmbH staff for their valuable contribution and in particular the Principal Investigator of the study, Dr. J. Sahlmann for his professionalism.

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