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Observational Study of a Multi-Active Ingredient Over-the-Counter Cold Remedy Following Active Pharmacist Recommendation

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Abstract

Real-world user satisfaction with a fixed dose combination over-the-counter cold remedy (Vicks Symptomed Complete Cytrynowy hot drink; VSCC) was evaluated in a prospective, non-comparative, observational study involving 176 pharmacies in Poland from February to April 2015. 1391 participants completed a questionnaire in the pharmacy and several paper questionnaires at home following use of the product at their own discretion. Participants returned their completed questionnaires to the pharmacy. 1356 participants were included in the intent-to-treat analysis. Participants highly valued the advice from their pharmacist (97%, $P < 0.0001$, important vs. not important) and thought the quality of that advice was good (93%, $P < 0.0001$, good/very good vs. very bad-fair). 96% of participants found VSCC to be effective in some way against their cold symptoms ($P < 0.0001$, effective vs. not effective) and 68% of them stated that it was better than any other cold therapy they had used before ($P < 0.0001$, better/best vs. same/worse). Adverse event reporting was very low.

Keywords

Common Cold, Upper Respiratory Tract Infection, Observational, Pharmacy, Over-the-Counter, Fixed-Dose Combination, Common Cold Symptoms

1. Introduction

1.1. Background

Acute upper respiratory tract infection (URTI) is one of the most common infectious diseases worldwide [1]. As such it represents a significant cost to society.

Studies from the United States [2] [3] confirm the magnitude of the economic cost of the common cold. It has been estimated that $25 billion every year is lost due to non-influenza common cold, of which $16.6 billion is lost on-the-job productivity, $8 billion is due to direct employee absenteeism and $230 million is due to caregiver associated costs [2].

Self-care and self-medication have attracted considerable international health-care policy interest because they effectively reduce the burden on health services. A large number of people make use of non-prescription over-the-counter (OTC) medicines for themselves or their children, and many health professionals in primary care settings recommend them to their patients as a first-line treatment for a range of non-serious conditions [4]. Pharmacists play an increasingly important role in patient care, in particular in the recommendation of non-prescription remedies. This is being shown to be beneficial to patients [5]. Pharmacists are becoming more patient oriented and are bringing many positive changes in lives of patients. There is mounting evidence that patient counseling and product recommendation by the pharmacist enhance patient satisfaction [6] and improve patient outcomes [7].

Acute URTI or common cold is caused by more than 200 known viruses which infect the tissues of the upper and/or lower airway causing a variety of local and systemic symptoms which can vary in severity and prevalence, but are generally self-limiting and infrequently lead to complications. There is no cure for the common cold hence the treatment is focused largely on OTC medicines to reduce symptom severity to maintain patient performance and quality of life [8] [9]. As such, multi-symptom relief cold remedies containing several active ingredients can provide advantages to the care-giver and patient when used as directed [10].

Vicks Symptomed Complete Cytrynowy (VSCC), available in many European Union countries with different licensed names, is an over-the-counter hot drink medicine licensed in Poland for short term symptomatic relief of mild to moderate pain, fever, nasal congestion and chest congestion associated with common colds and influenza. The active pharmaceutical ingredients (APIs) are paracetamol (500 mg), phenylephrine (10 mg) and guaifenesin (200 mg) which have a long history of safe and effective use for the relief of common cold or flu symptoms.

Paracetamol is a substance used for many years as an analgesic and antipyretic agent. Phenylephrine belongs to the class of α_1-adrenergic receptor agonists and activates receptors in the smooth muscles of blood vessels, causing vasoconstriction leading to decreased congestion and swelling of the nasal mucosa. The third component of VSCC, guaifenesin, is a substance with expectorant action. By stimulating receptors in the gastric mucosa, it causes a reflex increase in the volume of secretions in the airways and reduces mucus viscosity [11]. This facilitates expectoration, supports removal of the residual secretions to clear the airway [12] and promotes productive cough. Real-world patient satisfaction has not previously been assessed for this combination of APIs in a single hot drink re-

medy.

1.2. Objectives

This observational study was conducted to assess participant satisfaction with VSCC under conditions of normal purchase and use following active recommendation by a pharmacist. Secondary objectives were to evaluate the frequency of VSCC use over the duration of the study, to evaluate participant perception of the effectiveness of VSCC in relieving cold symptoms overall, and to assess the quality and importance of the pharmacist's advice when recommending VSCC.

2. Materials & Methods

This was a non-interventional, multicentre, open label, single product, prospective, non-comparative, observational study in adult participants with the symptoms of URTI who purchased VSCC in Polish pharmacies for their personal use.

The study was conducted between February and April 2015, in a manner consistent with the Declaration of Helsinki, European Union Directives 2001/83/EC and 2010/84/EU and Polish Act of 06 September 2001-"Pharmaceutical Law" (Journal of Laws from 2008, No. 45, item 271, including the 2013 amendment). Rules for conducting the study were subject to the guidelines of Polish Pharmaceutical Law (Art. 37) defining a non-interventional study as a study in which: 1) medicinal products are used in a manner specified in the marketing authorisation; 2) allocation of patients to the group which uses a particular therapeutic strategy is not defined by the trial protocol but depends on the current practice, and the decision to administer the medicine is clearly separated from the decision to include the patient in the study; 3) in patients, no additional diagnostic or monitoring procedures are carried out, and epidemiological methods are used to analyse the collected data. Ethics Committee approval was granted by the Medical University of Warsaw (Żwirki i Wigury 61 St, 02-091 Warsaw). All participants gave written informed consent. The Principal Investigator had full access to all collected data and statistical analyses.

2.1. Pharmacy Study Sites and Participants

Pharmacist investigators were recruited by the Clinical Research Organization (Bioscience S.A.) by telephone. 200 study sites were initially recruited however 24 sites withdrew during the study mainly citing that they were unable to implement the enrollment plan (lack of sufficient time to conduct the study and lack of participants meeting the inclusion criteria). 1391 participants were recruited into the study from the remaining 176 study sites.

2.2. Study Flow

Participants were served in a pharmacy in accordance with generally accepted professional standards, and recommendation of VSCC depended solely on medical indications and the independent decision of the pharmacist. Following purchase of VSCC, adult participants were provided with information about the

study and were asked by their pharmacist if they would like to enrol in the study.

Participants willing to enrol in the study signed Informed Consent and Data Processing Consent Forms developed in accordance with the legal requirements in Poland. If the participant met the Inclusion/Exclusion criteria they were recruited into the study. Participants were included if they were ≥18 years of age, were recommended VSCC for their own use by the pharmacy, and if they agreed to sign the Informed Consent. Volunteers were excluded if they had chronic cough or recurrent respiratory signs and symptoms, such as a persistent cough or chronic symptoms/disease of the respiratory tract or a contraindication to VSCC. The number of days the participant had been suffering from cold or flu symptoms at the time of medicine purchase was not collected. Participants were allowed to use any therapy they deemed necessary to control their symptoms while in the study and were informed they could stop taking VSCC at any time.

The pharmacist then collected basic demographic data of participants (excluding confidential personal identification data) and assigned identification numbers to them. Participants were immediately asked by their pharmacist to complete a paper diary ("Baseline" assessment) in the pharmacy. Then on the same evening ("Day 1") and for an additional two consecutive days ("Day 2", "Day 3") after purchasing VSCC participants were asked to complete a paper diary at home. All paper diaries included Wisconsin Upper Respiratory Symptom Survey (WURSS-44), a validated instrument for evaluating the quality of life in patients with symptoms of acute upper respiratory tract infections [13]. The Day 1 paper diary included an evaluation of the quality of the advice they received from the study pharmacist when discussing VSCC. They were asked to record their response on a 5-point scale ("Very bad", "Bad", "Fair", "Good", "Very good"). Participants were also asked to record in their Day 1 patient diary how important the advice from the pharmacist was in helping them treat their cold. They were asked to select from the following responses: "Not important", "Important", "Very important".

The Day 3 diary contained an end of treatment assessment which included a number of questions related to the participant's overall experience with VSCC. These questions included; "Are you satisfied by Vicks Symptomed Complete Cytrynowy?" with 3 possible responses provided ("Very satisfied", "Satisfied" and "Not satisfied"), "Was Vicks Symptomed Complete Cytrynowy effective in reducing your cold and cough symptoms?" with 5 possible responses provided ("Not effective at all", "Rather effective", "Effective", "Very effective", "Exceedingly effective"), "How likely would you be to recommend Vicks Symptomed Complete Cytrynowy to friends and family?" with 5 possible responses provided ("Definitely would recommend", "Probably would recommend", "Might or might not recommend", "Probably would not recommend", "Definitely would not recommend") and "How did Vicks Symptomed Complete Cytrynowy compare to other cough/cold/flu products you have used in the past?" with 6 possible responses provided ("This was the best cough/cold/flu medicine I have ever used", "This was better than most cough/cold/flu medicine I have used", "This was

about the same as other cough/cold/flu medicine I have used", "This was worse than other cough/cold/flu medicine I have used", "This was the worst cough/cold/flu medicine I have ever used", "Have not used cough/cold/flu medicine in the past"). The diary also contained the WURSS-44 instrument.

According to the Patient Information Leaflet and Summary of Product Characteristics for VSCC, up to 4 sachets can be taken in a single 24 hour period, 4 - 6 hours apart. Participants were asked to self-report their usage of VSCC over the 3 days of the study by recording the times per day that they used VSCC, and then the number of sachets they used in their diaries.

After treatment with VSCC was concluded, the participants mailed their completed diaries to the pharmacy. Participants were asked to contact the pharmacy if an adverse event was experienced and the study pharmacist took responsibility for recording and reporting adverse events.

At the beginning and end of their involvement in the study, the pharmacists were asked to complete their own assessments. In both assessments they were asked "How likely are you to recommend Vicks Symptomed Complete Cytrynowy for common cold patients?" In their pre-study assessment they were also asked for their reason(s) for choosing their response.

2.3. Statistical Methods

The intent-to-treat (ITT) population of participants that took product was used for all analyses. For day specific analyses the participant had to take product for the given day to be included in the analyses. For overall study analyses like patient impression of pharmacist advice or participant assessment of VSCC only taking product once during study would be needed to be included in the analyses. The change from baseline WURSS-44 total score was analyzed by a Wilcoxon signed rank test. A nonparametric test was chosen as the data violated normality. The participant impressions of pharmacist advice or participant assessment of VSCC were analyzed by binomial test categorizing the particular question into two groups dependent on question (Satisfied vs. Not satisfied, Effective vs. Not effective, etc.) and testing if differences exist between groups. SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for analyses. Hypotheses were tested at a two-sided significance level of 5%.

3. Results

3.1. Participants

The study was planned for the recruitment of 1000 participants from 200 participating pharmacies across Poland, however 1391 participants were actually recruited into the study by 176 pharmacists. 1356 participants were included in the ITT analysis (35 participants were excluded as there were no records of taking product over the 3 days). 62.4% of the participants were female (N = 821) and 37.6% were male (N = 494). The gender of 41 participants was not recorded. The youngest participant was 18 years old, the oldest one was 90 years (mean of 42 years and median of 38 years).

3.2. Concomitant Medications

Participants were asked to record the usage of any other medication on each day in their patient diary. 68.7% of participants (N = 901) declared that VSCC was the only medicine they used throughout the course of the study. The highest group of concomitant medications reported was other cold/flu remedies (N = 169), followed by medicines used in the long-term treatment of cardiovascular diseases e.g. β-blockers, angiotensin converting enzyme inhibitors, sartans, calcium channel blockers, nitric oxide derivatives, diuretics and also prophylactic and supplementary acetylsalicylic acid and potassium (N = 129). Medications for allergy/respiratory symptoms e.g. asthma (N = 32) comprised the third biggest group of concomitant medications.

3.3. Study Completion Rate

89.5% (N = 1213) of participants completed this 3 day study. The other participants withdrew from the study during the treatment (N = 141) or were lost to follow up (N = 2). The majority of the 143 participants who withdrew and specified the reason for their discontinuation reported that they did so because they believed they had recovered from their cold/flu (N = 104). The next frequently cited reason for discontinuation was a reported lack of efficacy (N = 23).

3.4. Adverse Events

On each day of their participation, participants had the opportunity to record adverse events in their diary. The question "Did you have other symptoms or problems from time of taking the last dose of Vicks Symptomed Complete Cytrynowy?" was answered "Yes" by 9 participants on Day 1, by 6 participants on Day 2, and by 7 participants on Day 3 to total 22 adverse events from 1356 participants included in the intent-to-treat analysis of the study (overall adverse event case reporting rate of 1.3%).

Only 3 participants then went on to report their adverse events to their pharmacist as instructed in their diaries. All 3 of these adverse event cases were classed by the pharmacist as being moderate in severity. However only 2 of the adverse event cases (skin rash, and nausea/palpitation/bad taste) were judged to be potentially associated with VSCC use. These 3 adverse event cases accounted for 0.2% of the 1356 patients. In each case, VSCC was discontinued and all symptoms were self-limiting with no other treatment required. No serious adverse events were reported.

3.5. Patient Reported Usage of VSCC

For Days 1, 2 and 3 the mean number of sachets used were 2.8, 2.8 and 2.6 respectively and this was broadly similar to the number of times that the participants said they used VSCC each day (Table 1). On Days 1, 2 and 3, 99.9% (N = 1354), 95.6% (N = 1296), and 89.1% (N = 1208) of participants respectively reported taking a least one sachet of VSCC. Very few participants (<1.2%) reported taking VSCC in excess of the recommended 4 times daily dosage.

Table 1. Participant reported usage of Vicks Symptomed Complete Cytrynowy.

	Mean (SD)		
	Day 1	Day 2	Day 3
How many times did you take Vicks Symptomed Complete Cytrynowy today?	2.7 (0.85) N = 1347	2.8 (0.72) N = 1290	2.5 (0.83) N = 1219
How many sachets did you take in total today?	2.8 (0.89) N = 1340	2.8 (0.80) N = 1279	2.6 (1.09) N = 1215
Number that took at least 1 sachet of Vicks Symptomed Complete	1354	1296	1208

N = number of subjects within specified study.

VSCC usage was similar over each day of the observation period (mean range of 2.6 - 2.8 sachets/day). The majority of participants took at least 1 sachet of VSCC on each day of the observation period.

3.6. Participant Assessment of the Pharmacist

In the Day 1 diary which was completed at home, participants were asked to evaluate the quality of the advice they received from their pharmacist on a 5-point scale. 93% of participants stated that the advice they received from the pharmacist was "Very good" or "Good" ($P < 0.0001$ vs. "Very bad-fair", Table 2).

In the Day 1 diary participants were also asked to consider how important the advice from the pharmacist was in helping them treat their cold. 97% of patients reported that the advice they received from their pharmacist about treating their cold with VSCC was "Important" or "Very important" ($P < 0.0001$ vs. "Not important", Table 2).

In the end of treatment assessment in the Day 3 paper diary 96% of participants reported that they were "Very satisfied" or "Satisfied" with their use of VSCC ($P < 0.0001$, vs. "Not satisfied", Table 3), 96% of participants reported that VSCC was at least "Rather effective" ($P < 0.0001$, vs. "Not effective", Table 3), 82% of participants reported that they would "Definitely" or "Probably recommend" VSCC to their friends and family ($P < 0.0001$, vs. "Unsure" or "Would not recommend", Table 3) and 68% of participants reported that VSCC was the "best" or "better than other cough/cold/flu medicines they have used" ($P < 0.0001$ vs. same-worse, Table 3).

3.7. WURSS-44

WURSS-44 total scores compared to baseline were used to gauge the effectiveness of VSCC in relieving multiple cold symptoms (Table 4). WURSS-44 median total scores were significantly lower at Day 1 (−12.0, $P < 0.0001$), 2 (−51.0, $P < 0.0001$), and 3 (−84.5, $P < 0.0001$) compared to a baseline median total score of 127.0.

3.8. Pharmacist Assessment of VSCC

In their first assessment which was completed prior to first participant recruitment

Table 2. Participant impression of pharmacist advice at Day 1 ITT (N = 1356).

	n (%)
How would you rate the advice that you were given when the pharmacist recommended Vicks Symptomed Complete Cytrynowy?	P < 0.0001[a]
1-Very bad	13 (1.0%)
2-Bad	3 (0.2%)
3-Fair	72 (5.4%)
4-Good	501 (37.6%)
5-Very good	743 (55.8%)
How important was the advice provided by pharmacist in helping you treat cold with Vicks Symptomed Complete Cytrynowy?	p < 0.0001[b]
1-Not important	36 (2.7%)
2-Important	644 (48.6%)
3-Very important	646 (48.7%)

N = number of subjects within specified study. n (%) = number and percentage of subjects within specified Parameter, study, and Category. [a]Testing good/very good (4 - 5) vs. very bad-fair (1 - 3)—93% good/very good (P < 0.0001). [b]Testing pharmacy advice important (2 - 3) vs. not important (1)—97% important (P < 0.0001).

the pharmacists (N = 172) were asked how likely they would be to recommending VSCC for common cold patients and to record the reasons for that choice. 76.7% recorded that they would "Most probably" recommend VSCC for common cold patients, 22.7% recorded that they would "Possibly" recommend VSCC and 1.2% recorded they were "Unlikely to recommend VSCC". The top two reasons recorded for those pharmacists who also recorded that they would "Most probably recommend VSCC" were "Effectiveness" (64.5%) and "Level of actives" (65.1%). At the end of the study the pharmacists completed another assessment. In this assessment 81.9% recorded that they were "Definitely" or "Very Likely" to recommend VSCC in the future for common cold patients.

4. Discussion

Common cold and flu infection of the upper respiratory tract results in multiple bothersome symptoms such as sore throat, headache, fever, muscle aches, runny nose, blocked nose and acute cough. In naturally occurring colds, sore throat has been shown to be a harbinger of the illness. It is often accompanied by multiple symptoms including nasal congestion (blocked nose), runny nose and headache with cough occurring less frequently but particularly bothersome when present later in the cold [14]. Common cold infection results in symptoms that rapidly increase in terms of severity, peaking 2 - 3 days after infection with a mean duration of 7 - 10 days. Cough can persist for more than 3 weeks [15]. The condition is generally self-limiting and most sufferers tend to recover without complications. Symptoms of uncomplicated cases of common cold and flu can be treated fairly easily with over-the-counter remedies to provide palliative relief without the need to see a physician.

Table 3. Participant assessment of Vicks Symptomed Complete Cytrynowy at Day 3 ITT (N = 1356).

	n (%)
Are you satisfied by Vicks Symptomed Complete Cytrynowy?	P < 0.0001[a]
1-Very satisfied	520 (39.2%)
2-Satisfied	746 (56.3%)
3-Not satisfied	59 (4.5%)
Was Vicks Symptomed Complete Cytrynowy effective in reducing your cold & cough symptoms?	P < 0.0001[b]
1-Not effective at all	56 (4.2%)
2-Rather effective	343 (25.8%)
3-Effective	346 (26.1%)
4-Very effective	410 (30.9%)
5-Exceedingly effective	173 (13.0%)
How likely would you be to recommend Vicks Symptomed Complete Cytrynowy to friends and family?	P < 0.0001[c]
1-Definitely would recommend	570 (43.0%)
2-Probably would recommend	510 (38.5%)
3-Might or might not recommend	194 (14.6%)
4-Probably would not recommend	30 (2.3%)
5-Definitely would not recommend	21 (1.6%)
How did Vicks Symptomed Complete Cytrynowy compare to other cough/cold/flu products you have used in the past?	P < 0.0001[d]
1-Best cough/cold/flu medicine I have ever used	233 (17.8%)
2-Better than most cough/cold/flu medicine I have used	655 (50.2%)
3-About the same as other cough/cold/flu medicine I have used	373 (28.6%)
4-Worse than other cough/cold/flu medicine I have used	37 (2.8%)
5-Worst cough/cold/flu medicine I have ever used	1 (<0.1%)
6-Have not used cough/cold/flu medicine in the past	7 (0.5%)

N = number of subjects within specified study. n (%) = number and percentage of subjects within specified Parameter, study, and Category. [a]Testing satisfied (1 - 2) vs. not satisfied (3)-96% satisfied (P < 0.0001). [b]Testing effective (2 - 5) vs. not effective (1)—96% effective (P < 0.0001). [c]Testing would recommend (1 - 2) vs. unsure or would not recommend (3 - 5)—82% would recommend (P < 0.0001). [d]Testing better/best (1 - 2) vs. same/worse (3 - 5) relative to other products—68% better/best than other products (P < 0.0001).

The aim of the present study was to observe participant satisfaction following use of VSCC following an active recommendation of the product by a pharmacist. 1000 participants were planned for recruitment, however slightly more were recruited than anticipated. The female to male patient ratio was approximately 2:1. As expected from an observational study, the age range of participants was broad (18 - 90 years of age). There was a high completion rate of the 3 day observation period (90%), with the main reason for study discontinuation being that the patient felt they were recovered from their cold/flu.

Compliance to the VSCC posology of not exceeding four doses or sachets in any 24 hour period was high and adverse event reporting was low, confirming

Table 4. Total score WURSS-44summary ITT (N = 1356).

	N	min	Mean (SD)	p25	median	p75	max	P-value
Baseline	1020	4	128.6 (62.4)	80.0	127.0	171.0	294	
Day 1	968	3	114.1 (61.1)	66.0	108.0	156.5	294	
Day 2	1009	0	72.8 (50.5)	34.0	63.0	103.0	294	
Day 3	1001	0	38.9 (37.8)	12.0	26.0	54.0	263	
Day 1 Change from Baseline	832	−119	−15.1 (24.7)	−29.0	−12.0	0.0	81	<0.0001
Day 2 Change from Baseline	845	−236	−55.5 (42.2)	−80.0	−51.0	−28.0	136	<0.0001
Day 3 Change from Baseline	842	−272	−90.7 (54.5)	−122.0	−84.5	−54.0	137	<0.0001

N = number of subjects within specified study group. P-value: Changes from baseline were compared to zero using Wilcoxon Signed Rank test within each study.

adherence to the labelling instructions for the product. Participants highly valued the pharmacist advice given to them at the point of VSCC purchase, with 97% reporting that the advice they received was "Important" and 93% reporting that the quality of the advice they received from the pharmacist was "Good" or "Very good". 96% of participants reported that they were "Satisfied" with their use of VSCC, 96% reported VSCC was "Rather effective in reducing cough and cold symptoms" and 68% stated that it was "Better than other cough/cold/flu products they had used in the past". We postulate that the pharmacist product recommendation was instrumental in driving compliance and may have positively impacted the participant's perception of product effectiveness.

The WURSS-44 instrument was employed in this 3 day observation study to assess the reduction in cold/flu symptoms. Median WURSS-44 total scores were significantly lower at Day 3 compared to baseline which is consistent with natural recovery from cold or flu infection. Just over 12% of participants reported the concomitant use of another cold medicine alongside VSCC, which is higher than anticipated but it is unclear how and why other cold medication was taken. According to the Special Warnings and Precautions for Use in the VSCC Summary of Product Characteristics, VSCC should be used with caution in individuals receiving digitalis, β-adrenergic blockers, methyldopa or other anti-hypertensive agents, and that conditions where these drugs are used are contraindications for the product. Almost 10% of participants reported concomitant use of medicines used for long-term treatment of cardiovascular disease such as β-blockers and perhaps should have been excluded from entry into the study. However given the observational, non-interventional design of the current study, these participants were recommended and used VSCC so they were not excluded from the ITT analysis.

There are several limitations of the study such as the uncontrolled design and natural self-resolution of common cold symptoms. Despite these, the magnitude of user reported benefit (satisfaction and effectiveness), compliance, perception of the value of the pharmacist advice and safety observation in a large, real-world population provides valuable information about VSCC and general reassurance on the value of multi-active, fixed-dose combination common cold therapy

to patients in the community.

5. Conclusion

This non-interventional, open-label, non-comparative, observational study demonstrated that individuals suffering symptoms of URTI were satisfied with their use of VSCC as a fixed dose combination over-the-counter cold remedy, were compliant to the dosing instructions and valued the product advice from their pharmacist. The study also provides reassurance on the safety of short-term usage of VSCC in a large community population.

Financial and Competing Interests

This work was sponsored in full by PGT Healthcare LLP. At the time of conducting this study and preparing this manuscript, GLP and JDH were full-time employees of The Procter & Gamble Company and may have stock and/or stock options in the company. GLP and JDH were responsible for study design and elements of study execution. GLP and JDH were responsible for the interpretation of the study results and initial manuscript drafting. BS was the Principal Investigator and Study Coordinator, and contributed to the development of the protocol. All attributed authors participated in the development and review of this manuscript.

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