Short-term Liver Safety of *Pelargonium sidoides* DC. Root (PELARGO) 20 mg Capsule: A Non-interventional Post-authorization Safety Study

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ABSTRACT

Background and Objectives. *Pelargonium sidoides* DC. Root (PELARGO) 20 mg capsule is approved by the Philippine Food and Drug Administration (FDA) for the symptomatic treatment of common cold. In compliance with FDA, this post-authorization safety study was conducted to determine the incidence of signs and symptoms of liver injury with PELARGO intake. It also aimed to look at symptom improvement and the incidence of other adverse events.

Methods. This non-interventional post-authorization safety study enrolled 300 adult patients with common cold, prescribed with *Pelargonium sidoides* DC. 20 mg capsule three times a day for seven days during routine clinical care from May 2023 to December 2023 in Cavite, Philippines. Demographic, clinical, and physical exam data were collected at baseline. Physical exam data, signs and symptoms of liver injury, symptom improvement, and other adverse events were determined post-treatment. Descriptive statistics were computed to characterize the participants at baseline (day 0) and end-study visit (day 8).

Results. There were 300 enrolled patients, 53% female and 60% single. The mean age was 36 years and the mean BMI was 26 kg/m^2. Vital signs at baseline were mostly within normal limits and most had respiratory findings. Two hundred ninety-eight (298) completed the study. Only a few had respiratory findings at end-study visit. There were no signs and symptoms of liver toxicity nor serious adverse events after seven days of PELARGO intake. Reported adverse effects with 2.0% to 1.3% incidence in seven days include dizziness, drowsiness, headache, and polyphagia. Others were <1% in incidence. Overall, adverse events were infrequent, mostly mild and of short duration, and resolved spontaneously. Most doctors (97%) and patients (98%) reported significant improvement of symptoms after treatment.

Conclusion. There is no evidence of liver toxicity after seven days of PELARGO intake for common cold among Filipino adults. The drug was well tolerated, and most patients experienced significant symptom improvement. Results should be interpreted with caution in the light of study limitations.

Keywords: Pelargonium, common cold, hepatotoxicity

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INTRODUCTION

In the Philippines, Acute Respiratory Infection was the top cause of morbidity from 2019-2023.[1] Common cold, a syndrome of upper respiratory symptoms: nasal congestion, sore throat, runny nose, cough, sneezing, headache, and malaise, is caused by over 200 different viral agents, most commonly rhinovirus.[2,3] Symptoms may occur as early as 10 to 12 hours after inoculation and usually lasts from seven to 10 days but may persist up to three weeks.[4,5]

Though relatively mild compared to other illnesses, common cold is one of the frequent reasons for missing work or school. A 2019 global study indicated that 2.25 episodes happened per individual per year.[6] On average, adults can have 2 to 4 colds per year while children have as many as 6 to 8.[2,7]

For centuries, indigenous people of South Africa used *Pelargonium sidoides* as a remedy for respiratory tract infections.[8] *Pelargonium sidoides* DC. Root extract has been marketed in Europe as a treatment for bronchitis and symptoms of common cold in the early 1990s and received full market authorization from the German drug regulatory agency in 2005.[9-13]

The European Medicines Agency evaluated *Pelargonium sidoides* as a symptomatic treatment for common cold based on its long-standing use.[14] Clinical studies on *Pelargonium sidoides* showed reduced duration and severity of acute respiratory tract infections,[15,16] specifically common cold[13,17]. Systematic reviews and meta-analyses support its efficacy and safety in the management of respiratory tract infections.[15-20]

In 2011, a total of 19 reports of adverse effects on the liver were recorded in the German spontaneous reporting system.[21] Symptoms of liver injury may include fatigue, loss of appetite, nausea, abdominal pain, jaundice, itching, and dark urine.[22] However, it remains controversial whether these events are indeed due to the drug.

Pelargonium sidoides (PELARGO) 20 mg capsule has been approved as a Traditionally-Used Herbal Medicine for the symptomatic treatment of common cold in the Philippines in 2022.[23] Since there are reports of possible risk of liver toxicity with its use, further evaluation was necessary, and the Philippine FDA mandated a post-authorization safety study. Hence, this study was conducted primarily to determine the incidence, and signs and symptoms of liver injury with PELARGO intake. It also aimed to look at symptom improvement and the incidence of other adverse events.

METHODS

Study Design

This was a non-interventional, observational, single-arm prospective follow-up study conducted in compliance with FDA post-authorization requirement. The design follows the latest EMA/813938/2011 Guideline on Good Pharmacovigilance Practices (GVP) Module VIII as required by the FDA for a post-authorization safety study. In this Guidance, a non-interventional post-authorization safety study is one where (1) the medicinal product is prescribed in the usual manner according to its marketing authorization, (2) the assignment of a patient to a treatment falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study, and (3) no additional diagnostic or monitoring procedures are applied to the patients and epidemiological methods are used for analysis of the collected data.[24]

The Protocol and Informed Consent Form were reviewed and approved by the Ethics Review Board of the University of the East Ramon Magsaysay Memorial Medical Center, Inc. Research Institute for Health Sciences (UERMMMCI-RIHS) prior to implementation. The design was concurred by FDA thru a letter from the Center for Drug Regulation and Research or CDRR (written communication, 28 September 2022) and, per FDA CDRR instruction (written communication, 21 March 2023), the Protocol was submitted to the agency as part of the Product's Risk Management Plan. It was sponsored by Pascual Laboratories Inc. through Pharmalytics Corporation, a Contract Research Organization (CRO) accredited by FDA. The sponsor funded the study and participated in the review and approval of both the Protocol and the Clinical Study Report (CSR). The CRO implemented the study. It also drafted the Protocol and CSR, and participated in their review and approval.

The primary objective was to determine the signs and symptoms of liver injury after intake of PELARGO 20 mg capsule, three times a day for seven days. Secondary objectives were to determine the incidence of other adverse events and the Global Assessment of Change by doctors and patients after treatment.

The active ingredient of PELARGO 20 mg capsule is an herbal extract of *Pelargonium sidoides* DC Root with ethanol 11% (m/m) as solvent and Drug to Extract Ratio (DER) of 4-25:1. EPs 7630, the formulation most cited in the literature, is an herbal extract with ethanol 11% (m/m) as solvent and DER of 1:8-10.[13] Both these extracts are in the European Union herbal monograph on *Pelargonium sidoides* DC. The dose of PELARGO 20 mg capsule used in the study is equivalent to the adult dose of the extract in EPs 7630 based on the monograph.[14]

The study flow diagram is presented in Figure 1. It was conducted from May 2023 to December 2023 in Cavite, Philippines. Three hundred Filipino patients who consulted as outpatients and prescribed by their attending physician with PELARGO for common cold were eligible to participate after giving their written informed consent. Aside from the labeled contraindications (hypersensitivity to *Pelargonium sidoides*, history of liver disease, pregnancy or lactation, and children under the age of 18 years), no other exclusions were made as this study follows routine clinical care. Data were collected over a period of one year to meet FDA timeline. Three hundred patients were recruited to be

able to estimate incidence rate of liver injury with a precision of 2.5% and a reliability of 95% assuming the true incidence of liver injury in the population was 5%. No operational definition of common cold was prescribed and doctors were allowed to diagnose the disease as they do in normal practice. The dose of the medicine used was 20 mg three times daily consistent with the label and patients were allowed to take concomitant medications as in normal practice.

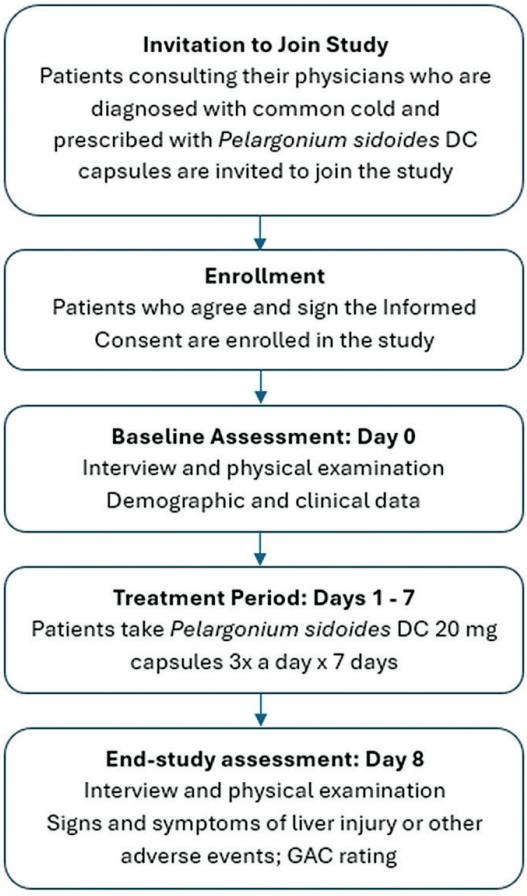

Figure 1. Study flow diagram.

On the patient's initial visit (day 0), interview and physical examination were conducted. Baseline information were collected including demographic and clinical data, and signs and symptoms related to liver injury (jaundice, dark urine, fatigue, weakness, nausea, poor appetite, right upper quadrant abdominal pain, fever, rash, and itching), and recorded in a Case Report Form (CRF). Vital signs and physical examination findings were also recorded in the CRF. The patients were instructed to take the medicine three times a day for seven days (with no restriction of timing with reference to meals, consistent with the FDA-approved product label) and record their intake in the Patient Study Card. They were also instructed to report to their doctor any adverse event that they may experience while taking the drug and asked to return for their last visit, after completion of treatment, on day 8.

At the patients' last visit, they were again interviewed and examined, especially for any sign or symptom of liver injury, and requested to assess the improvement of their signs and symptoms through an 11-point visual analog scale to determine Global Assessment of Change (GAC). GAC or Global Rating of Change (GRC) scales are commonly used in clinical research to quantify the patient's improvement or deterioration over time as scored on a numeric or visual analog scale.[25] Attending doctors were also asked to determine GAC by gauging the improvement or worsening observed in the patients during their last visit. The 11-point scale designed by the investigators ranges from "Very much worse" (-5) to "Very much better" (5) as illustrated in Figure 2. A positive change of at least 2 points was considered significant improvement.

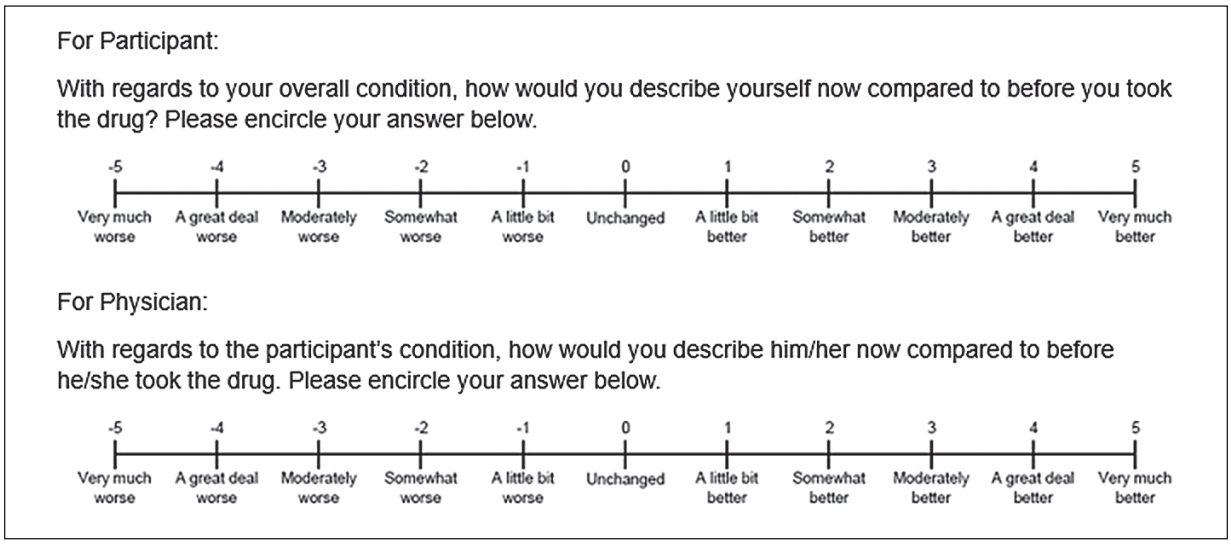

Figure 2. Global Assessment of Change Scale used in the study.

Other adverse events were collected by means of a standard question: "Did you have any health problems or symptoms since your previous visit?" These were recorded on the Adverse Event Form including seriousness, date of onset, duration, maximum intensity, action taken, outcome, and causality assessment. At the end of the visit, patients were asked to report to their doctor if they experience any post-study adverse event, especially any sign or symptom of liver injury.

Descriptive analysis was performed. Demographic data and clinical data were summarized using frequency distributions or measures of central tendency and variation (mean ± standard deviation and range). Frequency and incidence rates of the signs and symptoms of liver injury were determined. Frequency distribution was also used to describe the Global Assessment of Change Scores. No inferential statistics were done, this being an observational prospective follow-up study with no comparison group.

RESULTS

Study Population

Of the 300 Filipino patients enrolled, 298 completed the study while two failed to return for their second (end-study) visit. These two patients were both non-responsive to reminders on the second visit and when contacted after they failed to return, one cited "conflict with work schedule" and the other cited "work-related concerns." By virtue of the reasons given, they were not included in the end-study visit analysis. Exclusion of these missing data is not expected to substantially affect the safety picture. Aside from these, there were no other missing data in the study.

The demographic characteristics of the participants are presented in Table 1. Age averaged 36 years, ranging from 18 - 77. The most common age group was 18 – 29 years (39%) and majority (63%) were within 18 – 39 years old. Majority (60%) were single. Mean height was 157.56 cm, mean weight was 64.61 kg, and mean BMI was 26.08 kg/m^2. Close to a quarter (24%) had normal BMI and majority were either overweight (31%) or obese (38%). The distribution of demographic variables was descriptively similar in males and females.

Table 2 presents the medical and surgical history of the participants at baseline. More commonly they had histories of respiratory illnesses, especially acute rhinitis (12%). Twelve (4%) had hypertension. Surgically, 2% and 1% have had Caesarian section and cholecystectomy, respectively.

The baseline and end-study vital signs and physical exam findings are presented in Table 3. At baseline, average vital signs were normal with a minority of subjects having elevated

Table 1. Demographic Data of Participants, by Gender

Demographic characteristic	Frequency (%) or Value		
	Males (n=141; 47%)	Females (n=159; 53%)	Total (n=300)
Age (years)			
18 – 29	59 (42)	59 (37)	118 (39)
30 – 39	39 (28)	33 (21)	72 (24)
40 – 49	24 (17)	32 (20)	56 (19)
50 – 59	13 (9)	21 (13)	34 (11)
60 – 69	5 (4)	12 (8)	17 (6)
≥70	1 (<1)	2 (1)	3 (1)
Mean ± SD	35 ± 12	37 ± 14	36 ± 13
Range	18 – 73	18 – 77	18 – 77
Marital status			
Married	44 (31)	65 (41)	109 (36)
Single	95 (67)	86 (54)	181 (60)
Widow/Widower	2 (>1)	8 (5)	10 (3)
Height (cm)			
Mean ± SD	163.39 ± 9.46	152.35 ± 8.01	157.56 ± 10.31
Range	131.00 – 183.00	105.20 – 175.00	105.20 – 183.00
Weight (kg)			
Mean ± SD	68.79 ± 14.59	60.90 ± 13.58	64.61 ± 14.58
Range	42.60 – 120.00	37.00 – 111.00	37.00 – 120.00
Body Mass Index (BMI; kg/m^2)			
<18.5 (Underweight)	10 (7)	12 (8)	22 (7)
18.5 – <23 (Normal)	32 (23)	39 (25)	71 (24)
23.0 – <27 (Overweight)	46 (33)	48 (30)	94 (31)
≥27.0 (Obese)	53 (38)	60 (38)	113 (38)
Mean ± SD	25.81 ± 5.12	26.31 ± 5.96	26.08 ± 5.58
Range	16.33 – 38.58	16.33 – 51.34	16.33 – 51.34

SD – standard deviation

Table 2. Medical and Surgical History of Participants (n=300)

Medical and Surgical History of Participants	Frequency (%)
Most common medical conditions	
Acute rhinitis	35 (12)
Systemic viral illness	16 (5)
Colds	14 (5)
Hypertension	12 (4)
Acute tonsillopharyngitis	11 (4)
Most common surgical conditions [a]	
Caesarean section	6 (2)
Cholecystectomy	2 (1)

[a] *All females; Overall 14 females and three males had history of surgery for various conditions.*

Table 3. Baseline and End-study Vital Signs and Physical Exam Findings of Participants

Variable	Frequency (%) or Value	
	Baseline (n=300)	End-study (n=298)
Vital signs		
Temperature		
Mean ± SD[a]	36.37 ± 0.27	36.36 ± 0.28
Range	36.0 – 37.3	35.90 – 37.40
Pulse		
Mean ± SD	83.88 ± 9.70	84.19 ± 9.32
Range	53 – 117[b]	49 – 115[b]
Respiratory rate		
Mean ± SD	18.20 ± 1.73	18.00 ± 1.70
Range	14 – 25[c]	15.00 – 22.00[c]
Systolic blood pressure		
Mean ± SD	117.07 ± 13.62	115.79 ± 12.48
Range	90 – 180[d]	90 – 200[d]
Diastolic blood pressure		
Mean ± SD	79.59 ± 9.68	78.56 ± 8.14
Range	60 – 110[e]	60 – 110[e]
System with physical exam findings		
Eye, ear, nose, throat	290 (97)	14 (5)
Lungs	109 (36)	13 (4)
Extremities	2 (<1)	0 (0)
Heart	1 (<1)	0 (0)

[a] *SD – standard deviation*
[b] *10 (3%) at baseline and 8 (3%) at end-study have pulse rate >100/min*
[c] *17 (6%) at baseline and 13 (4%) at end-study have respiratory rate >20/min*
[d] *25 (8%) at baseline and 16 (5%) at end-study have systolic blood pressure >130*
[e] *77 (26%) at baseline and 46 (15%) at end-study have diastolic blood pressure >80*

values (see table footnotes). As expected, most had ear, nose and throat findings (97%) and many (36%) had lung findings. None had signs or symptoms related to liver injury (jaundice, dark urine, fatigue, weakness, nausea, poor appetite, right upper quadrant abdominal pain, fever, rash, and itching).

At end-study, average vital signs were also normal and descriptively, there were less elevated values (see table footnotes). Physical exam findings were less, with 5% having ear, nose, and throat findings, and 4% having lung findings.

Being an observational study that follows normal clinical practice, the participants were allowed to take concomitant medications, which are described in Table 4. Nearly half

Table 4. Concomitant Medication of Participants (n = 298)

Variable	Frequency (%)
Number of concomitant medications	
1	47 (16)
2	59 (20)
3	33 (11)
4 – 7	5 (2)
Total	144 (48)
Most common concomitant medications taken	
Paracetamol	58 (19)
Mefenamic acid	40 (13)
Ascorbic acid	21 (7)
PPA + Paracetamol	19 (6)
PPA + Chlorphenamine + Paracetamol	15 (5)

Table 5. Incidence of Signs and Symptoms of Liver Toxicity, n=298

Signs/Symptoms	Frequency	Incidence Rate in 7 days of treatment
Jaundice	0	0 per 298
Dark urine	0	0 per 298
Fatigue	0	0 per 298
Weakness	0	0 per 298
Nausea	0	0 per 298
Poor appetite	0	0 per 298
RUQ[a] abdominal pain	0	0 per 298
Fever	0	0 per 298
Rash	0	0 per 298
Itching	0	0 per 298

[a] *RUQ – Right upper quadrant*

(48%) took concomitant medications, more commonly one or two (36%). The most common concomitant medications were pain medications, namely paracetamol (19%) and mefenamic acid (13%).

Safety and Tolerability

Table 5 presents the incidence of signs and symptoms of liver toxicity after seven days of treatment with *Pelargonium sidoides* at 20 mg three times a day, while Table 6 presents the incidence of other adverse events among the subjects after the same treatment. There were no signs or symptoms of liver toxicity noted. Incidence was 0 per 298 patients in seven days of treatment (Table 5). Adverse events which were experienced by 0.3 to 2.0% of participants in seven days of treatment were mostly of mild severity and resolved spontaneously (Table 6). Dizziness, experienced by six out of 298 patients, was the most common though transient, lasting less than 21 minutes to one hour only. Drowsiness occurred in four patients with three lasting less than 5 minutes and one lasting for six days. Headache occurred in four patients with three lasting for less than three hours and one lasting for one day. Increased appetite was experienced by four patients lasting between four to six days. One incident of non-right upper quadrant abdominal pain was mild in severity lasting

Table 6. Incidence of other Adverse Events, n=298

Adverse Events	Frequency	Incidence Rate in 7 days of treatment
Dizziness	6	2.0%
Drowsiness	4	1.3%
Headache	4	1.3%
Polyphagia	4	1.3%
Non-RUQ[a] abdominal pain	2	0.6%
Nausea	2	0.6%
Diarrhea	2	0.6%
GERD[b]	1	0.3%
Dyspepsia	1	0.3%
Gastritis	1	0.3%
Increased blood pressure	1	0.3%
Bronchial infection	1	0.3%
Dyspnea	1	0.3%
Conjunctivitis, infective	1	0.3%
Mucositis, oral	1	0.3%

[a] RUQ – Right upper quadrant; [b] GERD – Gastroesophageal reflux disease

for 30 minutes only, and resolved without treatment, while a second was of moderate severity and lasted for three days. This patient had concomitant conjunctivitis and took antibiotics and steroids. Other non-serious adverse events with frequency of 2 or less are also shown in Table 6. There was no reported serious adverse event.

Global Assessment of Change

The Global Assessment of Change (GAC) or Global Rating of Change (GRC) scale offers a flexible, quick, and simple method of charting self-assessed clinical progress in research and clinical setting. This instrument has the advantages of clinical relevance, adequate reproducibility, and sensitivity to change and is intuitively easy to understand by the patient and the person administering.[25]

Figure 3 illustrates the results of GAC by participants and their doctors. Most of the participants (97.99%) noted a significant positive change of 2 points or more in Global Assessment of Change and 81.5% reported an even greater improvement of 4 or 5 points. Similarly, most doctors (96.98%) noted a significant positive change of 2 points or more and 87% reported an even greater improvement of 4 or 5 points. While more participants than physicians described change to be only moderately better, more physicians than participants described the change as a great deal better and even very much better. This is consistent with the earlier described physical exam findings (mostly in the ear, nose, and throat as well as lungs) found in most patients at the baseline visit and found only in a few at end-study visit (Table 3).

DISCUSSION

This study included 300 patients with common cold, prescribed with *Pelargonium sidoides* DC. Root (PELARGO) 20 mg capsule to be taken three times a day for seven days. After the seventh day, 298 patients were evaluated for safety and symptom improvement, and completed the study.

No signs and symptoms of liver injury (jaundice, dark urine, fatigue, weakness, nausea, poor appetite, right upper quadrant abdominal pain, fever, rash, and itching) were reported which was consistent with a 2012 study that concluded lack of evidence of hepatotoxicity with *Pelargonium sidoides*. Teschke and colleagues examined whether and to what extent was *Pelargonium sidoides* treatment associated with 13 reported liver injury cases. They conducted clinical evaluation and causality assessment using CIOMS scale which showed that none of the cases showed a positive signal of liver safety concern. The initial judgment of hepatotoxicity being caused by *Pelargonium sidoides* may have been due to confounding variables such as comedication with synthetic drugs, comorbidities, and lack of appropriate consideration of a differential diagnosis.[26]

No serious adverse events were reported while non-serious adverse events were infrequent (0.3 to 2.0% in seven days of treatment) and mostly mild and transient. Dizziness, the most common adverse event noted was also reported in cases from Germany.[27] Other adverse events noted such

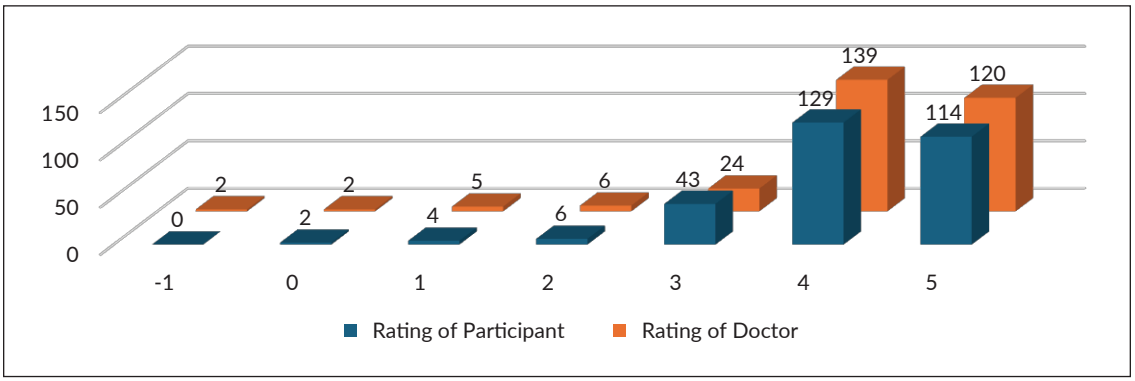

Figure 3. Global assessment of change as rated by participants and physicians.

as drowsiness, headache, nausea, diarrhea, non-right upper quadrant abdominal pain, dyspepsia, and dyspnea were also reported in different studies[12,27,28] which indicates consistency of patients' safety experiences across studies. The absence of new adverse events in this study suggests that the safety profile of *Pelargonium sidoides* DC. Root is already fairly well-defined by the existing studies. The low frequency, non-seriousness, and transient nature of most of the adverse events indicate that PELARGO has a tolerable adverse effect profile.

Four cases (1.3% in seven days) of increased appetite were reported as adverse events. In a study by Patiroglu and colleagues, an increase in appetite (p=0.022) was observed in subjects with upper respiratory tract infection (children with transient hypogammaglobulinemia of infancy), starting the fifth day of treatment with *Pelargonium sidoides* extract.[29] In the context of common cold, which also manifests with decreased appetite,[30] it is debatable if this should be considered an adverse event or a positive side effect, which would be an interesting subject of further investigation.

A total of 292 participants (97.99%) and 289 doctors (96.88%) noted a significant positive change of 2 points or more using the Global Assessment of Change indicating that most of the patients experienced symptom improvement with *Pelargonium sidoides*. A large majority of over 80% of patients and doctors reported even greater improvement of 4 or 5 points. This is in accordance with the results of a trial in 2007 that showed significant improvement ($p<0.0001$) from baseline to day 5 on the mean Sum of Symptom Intensity Differences (SSID) of 14.6 ± 5.3 points in the *Pelargonium* group compared to 7.6 ± 7.5 in the placebo group. After 10 days, 78.8% in the *Pelargonium* group were clinically cured compared with 31.4% in the placebo group ($p<0.0001$).[31] In a higher dose study after 10 days, 90.4% of the *Pelargonium* group were clinically cured compared to 21.2% of the control group ($p <0.0001$).[32]

Results of a meta-analysis showed that *Pelargonium sidoides* is significantly superior to placebo in improving the symptoms of common cold. Of the five trials included, patients treated with *Pelargonium sidoides* showed faster onset of action by a pooled difference to placebo. They also used significantly lower amounts of paracetamol and had more favorable outcomes on days 5 and 10.[17]

In a review by Brown, the incidence of side effects is extremely low at 0.53 per million defined daily doses.[33] A safety review in 2013 based on more than 8,000 patients given *Pelargonium sidoides* showed adverse event rates like those observed for placebo.[18] In 2019, a meta-analysis of safety data points to moderate rates of adverse events in general and of gastrointestinal complaints and epistaxis. However, compared with placebo, only a slight overall increase in the frequency of adverse events was observed. Adverse events potentially related to treatment were comparable between groups (*Pelargonium sidoides* vs. Placebo), and no serious adverse event occurred in any of the groups.[17]

This study was powered to detect an adverse event as low as 5% with a precision of 2.5% and a reliability of 95%. Under these conditions, there is no evidence of liver toxicity. Monitoring of signs and symptoms of liver injury and other adverse events was limited to the treatment period; less frequent adverse events or those that would occur after longer treatment periods may be undetected.

Several limitations arise from the design of the study which is a single-arm non-interventional post-authorization safety study. As earlier noted, the non-interventional design is prescribed by regulatory guidelines. As such, it does not allow the application of additional monitoring or diagnostic procedures not done in normal practice. Hence, no laboratory tests were done to determine the liver profile of the participants (consistent with normal practice) and the absence of signs and symptoms of liver injury could not be confirmed by laboratory data. Liver injury which are asymptomatic could not be detected. Further, as in normal practice, the participants were instructed by their physicians to report any adverse events that they experience, especially signs and symptoms of liver injury, even after the follow-up (end-study) visit, and none reported any. While this may indicate no liver injury post-study, this was not confirmed by patient examination since after the second visit, no monitoring visit was conducted, consistent with normal practice. It should be noted that the latency of liver injury may occur as early as five days from treatment to as late as three months.[34] While the study was able to determine the absence of signs and symptoms of liver injury immediately post-treatment, their absence could not be confirmed beyond that time. This is the main limitation of the study. The observation period is short-term without objective evidence of long-term liver safety. Thus, there is a need for further studies like long-term liver cohort studies and continuous post-marketing drug safety surveillance. Studies which are able to detect asymptomatic liver injury or early-stage liver injury are also warranted.

The single-arm design concurred by FDA and approved on ethics review prevents the conduct of comparisons between treated patients and non-treated patients, calculation of effect measures such as prevalence, risk, or odds ratios, and other related analyses (e.g., sensitivity analyses or controlling effects of confounders and effect modifiers). The absence of a control group and allowing patients to take concomitant medications for their illness, as in normal practice, should lead to interpreting the reported symptom improvement as the composite effects of the treatment, concomitant medications, and the natural course of the disease. In this study, 48% of the patients took concomitant medications, most commonly for pain. The incremental effect of these medications on both symptom improvement and/or adverse events could not be determined. The actual therapeutic effect of the drug in symptom improvement cannot be teased out from the total symptom improvement nor could it be separated from placebo effect due to the absence of a control group. Nonetheless, various controlled studies have

shown that PELARGO has significant therapeutic effect on top of the placebo effect as well as an acceptable safety profile.[10,12,13,17,18,28,31,32]

A possible limitation in the generalizability of the results since it was conducted in municipalities of Cavite, Philippines, may be unlikely because the population of Cavite is composed of Filipinos from practically all regions of the Philippines. The purposive manner by which the sample was taken could not ensure that a representative sample of the target population would be obtained in terms of demographic and clinical characteristics, hence limiting generalizability. However, the conduct of a study on randomly sampled patients from the entire country, or even just from the province of Cavite, was not feasible due to funding and time restrictions, as FDA mandated completion of the study and submission of the CSR within the 2-year initial marketing authorization given to the product.

CONCLUSIONS

Based on this study, no signs and symptoms of liver toxicity were observed in Filipino patients who took PELARGO 20 mg capsule three times a day for seven days. Reported adverse events were uncommon, non-serious, and mostly mild and transient. PELARGO has a tolerable adverse effect profile and is effective in improving symptoms of common cold in most patients. Results should be interpreted with caution in the context of the study's size, design limitations, and purely descriptive analysis, not being able to detect asymptomatic, rare, or late-onset liver toxicity. The single-arm and short-term nature of the study, although compliant with regulatory requirement, could not detect long-term liver safety or differentiate the actual therapeutic effect from other factors such as natural course, placebo effect, or concomitant medications. Better designed long-term studies and safety surveillance are warranted.

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Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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