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Comparative Study of Information Leaflets for Capecitabine-containing Oral Anticancer Preparations

Ko-ichi OHTAKI[1], Miyu TAKADA[1], Kuninori IWAYAMA[1], Ryo-o TANIGUCHI[2]

[1] Department of Pharmacology and Therapeutics, Hokkaido Pharmaceutical University, School of Pharmacy, Department of Pharmacotherapy & Therapeutics, Faculty of Pharmaceutical Sciences, Hokkaido University of Science
[2] Nakajima Pharmacy Ltd.

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Abstract

It is unclear whether patient-oriented instructional sheets (leaflets) for different capecitabine (Cape) products provide the same level of detail, and there have been no reports comparing the quality of Cape leaflets. Therefore, in this study, we compared the information provided in the leaflets for a brand product and generic versions of Cape, with the aim of identifying important information that must be present in a Cape leaflet and rating different leaflets based on the quality of information. We conducted an online questionnaire-based survey targeting pharmacists working at insurance pharmacies. The survey was conducted in the form of an anonymous questionnaire using Google Forms, targeting pharmacists working at Nakajima Pharmacy. There were 97 respondents (a 53.9% response rate), and 23.7% (23 pharmacists) of them reported using a leaflet when providing medication instruction for Cape. On the other hand, 51.5% (50 pharmacists) reported having no experience providing medication instruction for Cape. Importantly, with respect to hand-foot syndrome, one of the most critical side effects associate with Cape, pharmacists felt that patients should have a clear understanding of symptoms, particularly initial-stage symptoms; therefore, this information is of vital importance on Cape leaflets. In addition, 86.6% (84/97) of pharmacists responded that a Cape leaflet should include a photograph or illustration of the tablet, and 67.0% (65/97) of pharmacists responded that the leaflet should include a photograph of side effects; therefore, these were also considered necessary information for the leaflet. When comparing the ease of understanding information relating to the dosage and drug withdrawal period, side effects, and contraindications and drug interactions, the leaflets of certain generics drugs that were significantly easier to understand than that of the brand drug, whereas the leaflets of some generics were significantly more difficult to understand. In terms of ease of explanation to patients, the leaflets of certain generics were significantly better than that of the brand product, and there were also leaflets of generics that were more difficult to explain, suggesting the possibility that certain generics differ from the brand product in terms of information. When asked which leaflet they would choose to use for patient instruction, and which leaflet they thought would be useful to enable appropriate use of the drug, the pharmacists chose the leaflet of a generic over that of a brand product, whereas the leaflets of some of the other generics in the study were considered to be of a lower standard in these aspects. This study has been able to identify the types of information that are crucial to make an effective leaflet for a Cape product. The results of this study can be used as a guide when designing leaflets for Cape products in future.

Keywords

Capecitabine, Generic drugs, Patient information leaflets, Medication instructions

1. Introduction

Capecitabine (Cape) is an oral anticancer drug indicated in Japan for inoperable or recurrent breast cancer, colorectal cancer, and gastric cancer.[1)] Cape is a highly toxic drug that causes various side effects, such as hand-foot syndrome (HFS), and requires a withdrawal period.[2)] Careful medication instructions are required to ensure sustained treatment and improve adherence, as the duration of dosing and withdrawal periods vary depending on the cancer type and concomitant medications.[1)] If Cape is deemed sufficiently effective, pharmaceutical interventions would be essential to minimize side effects and enable uninterrupted treatment.[3)]

[1] 7-15-4-1 Maeda, Teine, Sapporo, Hokkaido 006-8585, Japan
[2] 2-15, North 10 Nishi 24, Chuo-ku, Sapporo, Hokkaido 060-0010, Japan
* Corresponding author: Ko-ichi Ohtaki, Department of Pharmacotherapy & Therapeutics, Faculty of Pharmaceutical Sciences, Hokkaido University of Science
Tel: 011-676-8658, Fax: 011-676-8666, E-mail: kohtaki@hus.ac.jp

Patient-oriented instructional sheets（leaflets）prepared by pharmaceutical companies are used as a tool for delivering appropriate medication instructions and are expected to increase adherence.

In Japan, the Action Program for the Promotion of the Safe Use of Generic Products[4] has been established, recommending the active use of generics to reduce healthcare costs. Generic Cape formulations have been available in the market since 2018, although their prices are relatively higher than those of other oral medicines. As treatment may be prolonged, the active use of generics may be sufficient to reduce healthcare costs. As of 2021, there are six generic versions of Cape on the market. However, drug prices have become the same for all six generics, making it difficult to select generics based on the price alone. Generic products are therapeutically equivalent to branded products; therefore, the content of patient information materials should at least be equivalent to that of branded products. However, the wealth of information accumulated during the period of development and before the launch of branded products generally gives them an edge over generics. Therefore, given the varied amount of information, there may be a difference between branded and generic products in terms of the content of patient-oriented materials.

There are several research reports comparing the formulation aspects of generic products with those of branded products.[5-8] However, only few studies have evaluated generics in terms of drug information, especially with regard to patient information materials. In Denmark, it has been reported that there are differences in the content of patient-oriented materials between branded products and generics for over-the-counter medicines.[9] In Japan, a comparative study of patient leaflets for the diabetes drug mitiglinide calcium hydrate by Akiyama et al. showed differences in the quality of information between brand-name and generic product leaflets;[10] however, this study did not examine anticancer drugs.　To our knowledge, no studies have evaluated or compared the quality of information in the leaflets of the brand-name and generic Cape formulations.

In this study, we conducted a questionnaire survey of pharmacists working in insurance pharmacies to compare leaflets of brand-name and generic products for Cape, a high-risk oral anticancer drug, to assist in product selection and to obtain further clarity on the necessary information to be included in leaflets of Cape products, referring to the method of Akiyama et al.[10] The survey was conducted via a web-based questionnaire. An oral chemotherapy management service provided by pharmacists has been reported to be effective in delivering early interventions, resulting in decreased rates of adverse effects, nonadherence, drug interactions, and medication errors over time.[11] Among the side effects of Cape, HFS is a serious dose-limiting toxicity, and grade 3/4 toxicity can lead to dose reduction or discontinuation of treatment.[12] Therefore, in this study, we modified the survey conducted by Akiyama et al.[10] and incorporated questions related to symptoms that patients should understand when receiving instruction on HFS and need for photographs of HFS, as well as questions related to dosage and drug withdrawal periods, side effects, and contraindicated drugs and drug interactions.

2. Methods

2.1. Survey period and facilities surveyed

The survey was conducted from July 13 to July 31, 2021, among a total of 180 pharmacists working across different outlets of Nakajima Pharmacies, a chain of insurance pharmacies with outlets in Hokkaido, Japan.

2.2. Questionnaire survey details

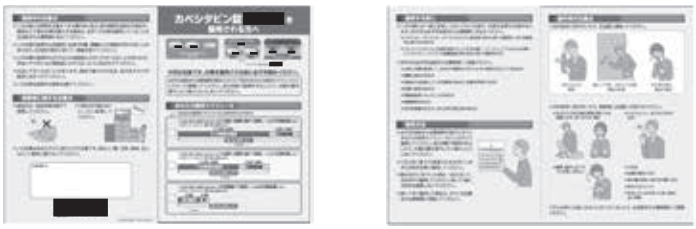
The survey was an unsigned, multiple-choice questionnaire prepared using Google Forms and sent to the subjects by email, together with the URL of a full-size sample of each leaflet. The leaflets included those of the brand-name drug Xeloda® tablets（Chugai Pharmaceutical Co., Ltd., Osaka, Japan）and five generic drugs（A–E）. The products of a particular company, for which leaflet-style instruction notes were not prepared, were excluded（Fig. 1）. The questions included in the questionnaire are presented in Table 1. As this survey was conducted in Japanese, Table 2 shows the questions asked in the Japanese questionnaire.

brand

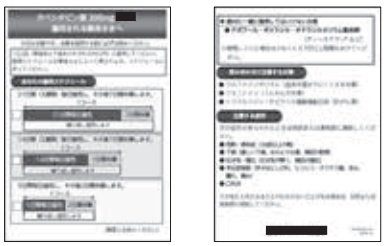
A

B

C



D



E

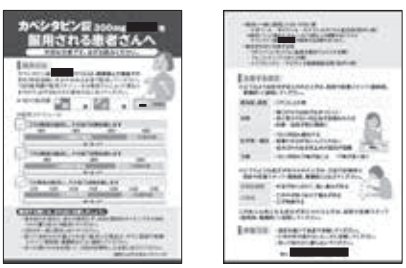


Fig. 1　Leaflets of the capecitabine products

The leaflets of the capecitabine brand produt and five generics（**A**, **B**, **C**, **D**, and **E**）. There were two types of leaflets for the brand drug according to dosage and withdrawal periods, and three types of leaflets for '**A**' according to dosage.

Table 1　Questionnaire content

1. Do you use leaflets when instructing on capecitabine tablets?
Choices：yes, no, no instructing experience

2. When pharmacists provide instruction on hand-foot syndrome symptoms, please select the most important symptoms that you would like patients to understand, in order of priority, from 1 to 5.
Choices：numbness, unusual sensations when touching things, tingling sensation, swollen, redness, skin dryness, skin pigmentation, nail deformities/peeling, skin peeling/sores, blister

3. For each leaflets, please select one that applies to whether the dosage and withdrawal periods are written in a way that is easy for patients to understand.
Name of pharmaceutical company：brand-name drug manufacturer, company **A-E**
Choices：easy to understand, slightly difficult, difficult

4. For each leaflets, please select one that applies to whether the side-effect symptoms are described in text or illustrations that are easy for patients to understand.
Name of pharmaceutical company：brand-name drug manufacturer, company **A-E**
Choices：easy to understand, slightly difficult, difficult

5. For each leaflets, please select one that applies to whether contraindications and interactions are written in a way that is easy for patients to understand.
Name of pharmaceutical company：brand-name drug manufacturer, company **A-E**
Choices：easy to understand, slightly difficult, difficult

6. For each leaflets, please select one that applies to the ease of explaining the information to the patient.
Name of pharmaceutical company：brand-name drug manufacturer, company **A-E**
Choices：easy to explain, slightly difficult to explain, difficult to explain

7. Are photographs or illustrations of tablets required on the leaflet for capecitabine tablets?
Choices：necessary, unnecessary

8. Is a photograph of hand-foot syndrome required on the leaflet for patients on capecitabine tablets?
Choices：necessary, unnecessary

9. Of the six types of leaflets, which would you choose to use for patient instruction? Please rank them in the order in which you would prefer to use them.
Name of pharmaceutical company：brand-name drug manufacturer, company **A-E**
Choices：1st～6th place

10. Which of the six types of leaflets are considered useful in terms of appropriate use? Please rank them in order of usefulness.
Name of pharmaceutical company：brand-name drug manufacturer, company **A-E**
Choices：1st～6th place

This survey was conducted in Japanese using Google Forms. The survey form in Japanese is shown in Table 2.

Table 2　Questionnaire in Japanese

１．カペシタビン錠の服薬指導時に患者用指導箋を使用していますか？
○　はい　　○　いいえ　　○　指導経験がない

2. 薬剤師が手足症候群症状の指導を行う際、患者に理解してほしいと考える重要な症状・文言を優先順位の高い順に1～5番に該当するものを選択してください。

	しびれ	ものに触れたときに普段とは違う感覚	ひりひりちくちく感	腫れ	赤み	乾燥	色素沈着	爪の変形・はがれ	皮膚のはがれ・ただれ	水膨れ
1番目	○	○	○	○	○	○	○	○	○	○
2番目	○	○	○	○	○	○	○	○	○	○
3番目	○	○	○	○	○	○	○	○	○	○
4番目	○	○	○	○	○	○	○	○	○	○
5番目	○	○	○	○	○	○	○	○	○	○

3. 各メーカーの指導箋について、用法用量や休薬期間は患者が理解しやすく書かれているかについて当てはまるものを1つずつ選んでください。

	理解しやすい	やや難しい	難しい
先発品	○	○	○
A社	○	○	○
B社	○	○	○
C社	○	○	○
D社	○	○	○
E社	○	○	○

4. 各メーカーの指導箋について、副作用症状は患者が理解しやすい文章やイラストで書かれているかについて当てはまるものを1つずつ選んでください。

	理解しやすい	やや難しい	難しい
先発品	○	○	○
A社	○	○	○
B社	○	○	○
C社	○	○	○
D社	○	○	○
E社	○	○	○

5. 各メーカーの指導箋について、禁忌薬や相互作用は患者が理解しやすく書かれているかについて当てはまるものを1つずつ選んでください。

	理解しやすい	やや難しい	難しい
先発品	○	○	○
A社	○	○	○
B社	○	○	○
C社	○	○	○
D社	○	○	○
E社	○	○	○

6. 各メーカーの指導箋について、患者への説明のしやすさについて当てはまるものを1つずつ選んでください。

	説明しやすい	やや説明しにくい	説明しにくい
先発品	○	○	○
A社	○	○	○
B社	○	○	○
C社	○	○	○
D社	○	○	○
E社	○	○	○

7. カペシタビン錠の患者向け指導箋に錠剤の写真やイラストは必要ですか？
○　必要　　○　不要

8. カペシタビン錠の患者向け指導箋に手足症候群の写真は必要ですか？
○　必要　　○　不要

9. 6種の指導箋の中で、あなたが患者指導に使うとしたらどれを選びますか。使いたい順に順位をつけてください。

	1位	2位	3位	4位	5位	6位
先発品	○	○	○	○	○	○
A社	○	○	○	○	○	○
B社	○	○	○	○	○	○
C社	○	○	○	○	○	○
D社	○	○	○	○	○	○
E社	○	○	○	○	○	○

10. 6種の指導箋の中で、患者の適正使用において有用と考えられるものはどれですか。有用な順に順位をつけてください。

	1位	2位	3位	4位	5位	6位
先発品	○	○	○	○	○	○
A社	○	○	○	○	○	○
B社	○	○	○	○	○	○
C社	○	○	○	○	○	○
D社	○	○	○	○	○	○
E社	○	○	○	○	○	○

This table shows the survey form in Japanese. Circles in the questions indicate radio buttons on the Google form.

2.3. Tabulation of questionnaire and statistical analysis

Responses to Question 2 of the questionnaire were scored in order of priority: 5 points for the first choice, 4 points for the second, 3 points for the third, 2 points for the fourth, and 1 point for the fifth, and the scores for each symptom were totaled across responses of individual pharmacists. We also investigated whether the symptoms mentioned in Question 2 were listed on each leaflet. In Questions 3-6, slightly difficult/slightly difficult to explain was replaced with difficult/difficult to explain, and the binary categorical variables of easy to understand/easy to explain and difficult/difficult to explain were used to compare the brand-name and each generic product using a chi-square test. For Questions 9 and 10, an ordinal variable with 6 points for first place, 5 points for second place, 4 points for third place, 3 points for fourth place, 2 points for fifth place, and 1 point for sixth place was used to compare the mean scores for the brand-name and each generic product using Welch's t-test. The significance level for all tests was set at $p < 0.05$. JMP® Pro 16.2.0 (SAS Institute Inc., Cary, NC, USA) was the statistical analysis software used.

2.4. Ethical considerations

This study was conducted in compliance with the Ethical Guidelines for Medical Research Involving Human Subjects and with the approval of the Ethics Committee of Hokkaido University of Science (application no. 21-06-011).

3. Results

3.1. Questionnaire response rate and use of Cape leaflets

A total of 97 respondents completed the questionnaire, yielding a response rate of 53.9% (97/180). Overall, 23.7% (23/97) of the respondents reported using leaflets prepared by pharmaceutical companies when giving instructions to patients, 24.7% (24/97) said they did not, and 51.5% (50/97) said they had no experience with giving instructions for Cape.

Table 3　Status of symptoms on each leaflet

	brand	A	B	C	D	E
tingling sensation	○	○	○		○	
unusual sensations when touching things				○		
numbness		○	○		○	
swollen	○	○	○	○	○	○
redness	○	○	○	○	○	○
skin peeling/sores						
skin dryness	cracking		cracking			
nail deformities/peeling						
blisters	○		○			
skin pigmentation						

The table shows the description of symptoms in Question 2 for each leaflet. If the corresponding symptom was listed in each leaflet, a circle was placed in the column for that symptom. Symptoms of cracking are shown in the table as "cracking" to be included in skin dryness.

3.2. Symptoms about HFS that patients should understand

Table 3 shows the status of each symptom (listed vs not listed) on each leaflet, and Fig. 2 shows the total score for each symptom based on the response to Question 2. Regarding the most important symptom that pharmacists wanted patients to understand when educating them on the symptoms of HFS, the most common answer was “tingling sensation,” followed by “unusual sensation when touching things,” and “numbness” (Fig. 2).

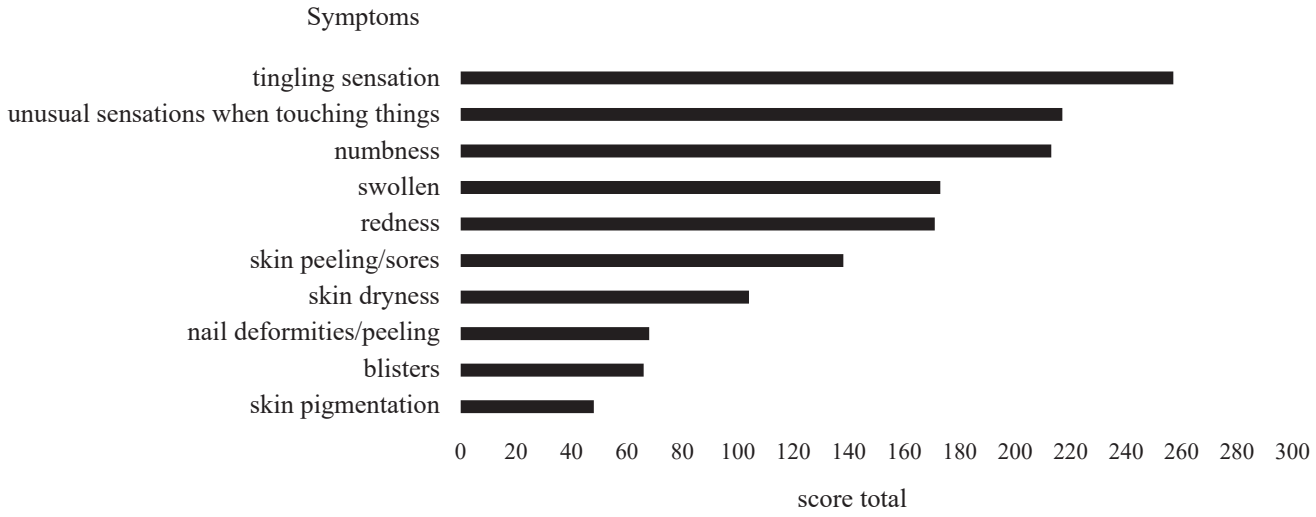


Fig. 2 Important symptoms and statements about hand-foot syndrome（HFS）that pharmacists want patients to understand

Graph representing the total score of individual symptoms based on the priority ratings given by the pharmacists in Question 2 of the questionnaire. The symptoms related to HFS were scored as follows: first, 5 points; second, 4 points; third, 3 points; fourth, 2 point; and fifth, 1 point.

3.3. Evaluation of leaflets and ease of explaining leaflets

Table 4 shows the responses to Questions 3–6 for the leaflets of the brand product and generics, with a *p* value indicating whether differences were significant compared with leaflet of the brand product. For information regarding dosage and withdrawal periods, the leaflets of **C** and **D** were significantly more difficult than that of the brand product（Question 3）. For information regarding the side-effect symptoms, the leaflets of **A**, **B**, **C**, and **E** provided details in text and illustrations that were

Table 4 Comparison of the evaluation of the leaflets for the brand product and each generic product in Questions 3-6

Question 3

	easy	difficult	*p* value vs brand
brand	76	21	
A	86	11	0.053
B	65	32	0.076
C	59	38	0.008**
D	57	40	0.003**
E	70	27	0.318

Question 4

	easy	difficult	*p* value vs brand
brand	57	40	
A	82	15	<0.001**
B	82	15	<0.001**
C	73	24	0.014 **
D	40	57	0.015**
E	70	27	0.050*

Question 5

	easy	difficult	*p* value vs brand
brand	66	31	
A	78	19	0.049*
B	62	35	0.544
C	46	51	0.004**
D	70	27	0.531
E	66	31	1.000

Question 6

	easy to explain	difficult to explain	*p* value vs brand
brand	71	26	
A	88	9	0.002**
B	72	25	0.870
C	60	37	0.092
D	53	44	0.007**
E	67	30	0.526

*$p < 0.05$, **$p < 0.01$

The table shows the responses to each of Questions 3-6. For each question, each response from **A** to **E** was compared to that of the brand product. In making the comparisons, responses of slightly difficult/slightly difficult to explain were replaced by responses of difficult/difficult to explain and compared as binary categorical variables. Statistical analyses was performed using the chi-square test.

significantly easier for patients to understand than the leaflet of brand product, whereas the leaflet of **D** was significantly more difficult to understand than that of the brand product (Question 4). For information regarding contraindications and interactions, the leaflet of **A** was significantly easier to understand than that of brand the product, whereas that of **C** was significantly more difficult for patients to understand (Question 5). In terms of the ease of explaining the leaflets to patients, respondents indicated that the leaflet of **A** was significantly easier to explain than that of the brand product, whereas that of **D** was significantly more difficult to explain than that of the brand product (Question 6).

3.4. Inclusion of photographs and illustrations of tablets and side effects on leaflets

When asked whether photographs or illustrations of tablets are required on the leaflets of Cape products, 86.6% (84/97) of the pharmacists said they were. In addition, 67.0% (65/97) of the pharmacists answered that it is necessary to include photographs of side effects in the leaflets used during medication instruction.

3.5. Usefulness of leaflets for instructing patients and ensuring proper use

Table 5 shows the results of the comparison of mean scores between the leaflet of the brand product and those of the generics in Questions 9 and 10. Regarding which leaflet would be chosen for instructing patients (Question 9), the mean score for the leaflet of **A** was significantly higher than that of the leaflet of brand product, whereas the mean scores for the leaflets of **C**, **D**, and **E** were significantly lower than that of the leaflet of the brand product. Regarding which leaflet would be considered useful for ensuring proper use (Question 10), the trend was similar to that noted in Question 9, with the mean score for leaflet of **A** being significantly higher than that of the leaflet of the brand product, whereas the leaflets of **C**, **D**, and **E** had significantly lower mean scores than that of the brand product.

4. Discussion

This survey aimed to compare the leaflets of the branded and generic Cape products and to obtain further clarity on the necessary information to be included in leaflets of Cape products. First, when asked whether they used the leaflets prepared by pharmaceutical companies, approximately half of the respondents had no experience with instructing patients about Cape. Furthermore, only about half of those who had experience instructing at Cape had used leaflets prepared by pharmaceutical companies. One possible reason for this was that individual pharmacies were providing medication instructions using only their own medication information forms.

Fluoropyrimidine drugs, typified by Cape, cause HFS, a dose-limiting toxicity. Its initial symptoms include abnormal sensations such as numbness, or

Table 5　Comparison of average scores between the brand product and each generic product in Questions 9 and 10

Question 9

	mean of scores	SD	*p* value vs brand
brand	4.12	1.75	
A	4.96	1.16	<0.001**
B	3.95	1.09	0.403
C	2.84	1.56	<0.001**
D	1.90	1.05	<0.001**
E	3.23	1.64	<0.001**

Question 10

	mean of scores	SD	*p* value vs brand
brand	4.23	1.75	
A	5.04	1.10	<0.001**
B	3.86	1.20	0.086
C	2.78	1.47	<0.001**
D	1.91	1.05	<0.001**
E	3.19	1.58	<0.001**

*$p < 0.05$, **$p < 0.01$,
The table shows the results of the responses to Questions 9 and 10. For each question, the mean score and standard deviation are shown as an ordinal variable with 6 points for first place, 5 points for second place, 4 points for third place, 3 points for fourth place, 2 points for fifth place, and 1 point for sixth place, depending on the response. The mean scores of the brand name and each generic were compared. Welch's t-test was used for statistical analysis.
SD: Standard deviation.

tingling.[13] This survey showed that pharmacists consider these as the key symptoms and statements they want patients to understand about HFS; in other words, they were aware that accurately communicating the initial symptoms is important in combating HFS; however, these symptoms are not listed in all leaflets (Table 3). Once Cape-induced HFS develops, it significantly impairs quality of life;[14] therefore, it is considered necessary to improve the descriptions of side-effect symptoms of HFS in the leaflets of Cape products prepared by pharmaceutical companies, with particular emphasis on the initial symptoms.

Questions 3–5 inquired about the ease of understanding of each instruction, focusing on dosage and withdrawal periods, side-effect symptoms, and contraindications and interactions. The responses to Questions 3–5 revealed that leaflets of some of the generics were more difficult to understand than that of the brand product, whereas leaflets of some of the other generics were easier to understand in terms of side-effect symptoms, and contraindications and interactions. In other words, it is possible that the leaflets of certain generics provide a different quality of information compared with that of the brand product in terms of dosage and administration, withdrawal period, adverse drug reactions, and contraindications and interactions.

Question 6 investigated the ease of explaining the content of the leaflets to patients. The leaflet of **A** was significantly easier to explain than that of the brand product. The leaflet of **A** was also easier to understand than that of the brand product both in terms of side-effect symptoms in Question 4 and contraindications and interactions in Question 5. This is thought to be the reason the leaflet of **A** was easy to explain. On the other hand, the leaflet of **D** was significantly more difficult to explain than that of the brand product. The leaflet of **D** was also more difficult to understand than that of the brand product both in terms of dosage and withdrawal periods in Question 3 and side-effect symptoms in Question 4, which may have contributed to the overall difficulty in explaining the contents of the leaflet.

When asked whether photographs and illustrations of tablets on leaflets are necessary, approximately 85% of respondents believed they were, indicating the high need for photographs and illustrations of tablets instructing patients on drug administration. In addition, when asked whether photographs of HFS are required on Cape leaflets, approximately two-thirds of respondents said they were. None of the leaflets surveyed in this study included photographs of HFS. However, it can be said that when instructing patients on medication, pharmacists consider it important to show photographs of HFS, a side effect for which care is critical for the continuation of treatment with Cape. Nonetheless, according to the survey results, the need for photographs of HFS on leaflets was not higher than that for photographs or illustrations of tablets.

When asked which of the leaflets they would choose to use for providing instruction to their own patients, respondents were significantly more willing to use the leaflet of **A** than that of the brand product. On the other hand, respondents were significantly less willing to use the leaflets of **C**, **D**, and **E** than that of the brand product. This suggests that there is a difference in the ease of use perceived by pharmacists in the field between the leaflets of the brand product and generic products of Cape. Furthermore, when asked which of the leaflets were considered effective in enabling the proper use of Cape, the responses were similar to those received for the abovementioned questions regarding the leaflets they would prefer to use for patient instruction. This suggests that there are differences not only in ease of use but also in usefulness for proper use among the leaflets.

A limitation of this study is that it included pharmacists only; hence, it does not reflect the opinion of patients on whether the information was easy to understand. We hope that future surveys consider the opinions of patients to further contribute to the improvement of leaflets of Cape products.

In this study, we compared the information on the leaflets for the brand-name and generic versions of Cape to assist in product selection and to obtain further clarity on the necessary information to be included in leaflets of Cape products, through

a questionnaire of pharmacists at insurance pharmacies in Hokkaido. Generic products are approved for marketing authorization on the basis that they are therapeutically equivalent to the brand-name product; however, the quality of information in the leaflet of generics should also be equal to that of the brand product. Therefore, in the future, it is desirable to prepare leaflets that are easy to explain and useful for providing information to patients when giving medication instructions.

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6. Conflict of interest

No conflicts of interest to be disclosed.

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