Final Report of the Test Results

Title

Test for primary skin irritation and hypersensitivity
of human subjects after 24 hour single application

Testing requested by: CDW Life Science Limited

Testing Agency : S2 Research Lab. Co.,Ltd.

S2 Research Lab.

Testing Report Number: 24CP-1480
Period of Test conducted: October 5 to October 7, 2020
Date of Issue of the Report: October 21, 2020
Report created by: S2 Research Lab. Co.,Ltd.

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1 Test Overview

Test Objective	To evaluate the primary skin irritation and hyper sensitivity of human subjects.
Examination Requirement	24 hour closed human patch test (20 test subjects)
Testing Samples and Tools Used	Be・vernal Pasted the testing sample 'as is' Two following types of medicine were used as test comparisons 1. Saline solution (Otsuka Pharmaceutical Co.,Ltd.) 2. White Vaseline (Taiyo Pharmaceutical Co.,Ltd.) We have used "allergEAZE Patch Test Chamber" (Smart Practice Japan) as patch test units.
Test Subjects	We have selected Japanese males and females who are between 20 and 59 years of age who do not conflict with the following exclusion criteria. In addition, we have obtained an agreement in writing from the test samples in advance for this test. *Exclusion criteria Those who show some irritation such as rash or bruises on the patch test area on the skin Those who have been using some medicine externally on the skin area within the last week before the test sample will be used where the patch test will be Those whom the doctors deem as inappropriate as test samples for this test.
Testing Method	We check for the eligibility of the testing samples' skin on the first day of the test. We have applied the testing sample on the patch test and conducted a 24 hour close patch test on the upper arm. We eliminated the patch test unit on the second day of the test (after 24 hours). 30 minutes after that and another 24 hours later (Test day three), we have evaluated the reaction of the skin on the applied area. We adhered to Chapter Four of the human patch test (p. 176) from (Cosmetics, Over the Counter Drugs Manufacturing and Selling Guidebook 2011-12). However, the number of test subjects was 20.
Evaluation Methods and Result Report	Dermatologists have evaluated according to the Japanese national standards 3). We have calculated the skin stimulation index based on the decision criteria according to the Sugai method 24 hours later and 48 hours later, and we assessed on safe products, tolerated products, products that require improvement and hazardous products. Test results will be reported via email as a quick report the next working day after the test completion, and the final test report will be sent within two weeks.
Test Result	The evaluation of skin sensitivity of Be・vernal was categorised as a Safe products.

2 Test Design

24 hour Closed Patch Test

We adhered to Chapter Four of the human patch test (p. 176) from (Cosmetics, Over the Counter Drugs Manufacturing and Selling Guidebook 2011-12).
However, the number of test subjects was 20.

3 Test Objective

We have evaluated the safety of the testing sample by gauging the primary skin irritation of the skin that will occur when it contacts the skin.

4 Test Subjects

4.1 Selection Criteria

We have incorporated those who qualify for all of the following criteria into this test.

Japanese males and females that are between the ages of 20 and 59 years old.
Those who have provided consent in writing prior to starting the test.
Those who are capable of following the instruction of the test and those who are able to turn up on the indicated date.

4.2 Exclusion Criteria

The exclusion criteria for this test are as follows:

Those who show skin irritation such as rashes or bruises on the area which is planned to be covered with the patch test
Those who have been applying medicine externally within the week of the use of the testing sample on the same aforementioned area
Those who show some allergic or other extreme reactions to materials such as tape
Those who have an uncontrollable systematic disease
Others whom the doctors deem to be inappropriate as testing samples.

4.3 Consent by the Test Subjects

We have explained about the following topics to the test subjects and obtained consent in writing with regards to participating in the test.

Objective of the test
Methods of testing
Expected potential side effects
Matters that test subjects are required to follow
Participation in the test is completely up to the free will of the test subject and he or she is free to withdraw at any point
Appropriate treatment and remedies that test subjects are open to receive in case

there are health issues that occur in the test.
The right to view and store the test results of the test subjects which the client that commissioned the test and the manager of the test have. Strict confidentiality of the test subjects' details will be preserved. Only the results of the test will be disclosed but the confidentiality of the test subjects will be maintained.
The test subjects can contact if they require more information about this test or if any damage to their health may arise.
The detail about any monetary incentive if test subjects are to be paid.

5 Storage and Maintenance of Testing Samples

The testing samples have been stored in a safe place and were used only under the restricted conditions that were given for the test proposal exclusively to the test subjects of this test.

6 Testing Methods

6.1 Application Method and Schedule

Day One of the Test
The suitability of the test subjects' skin was checked.
Some amount of the testing material was applied on the patch test units, and the units were applied to the backs or the upper arms of the test subjects and they were sent home.

Day Two of the Test (24 hours Later)
The patch test units were removed from the test subjects, and the areas where the patches were applied were marked.
The skin reaction was evaluated, and the test subjects were then sent home.

Day Three of the Test (48 hours Later)
The skin reaction of the marked area was evaluated.

6.2 Decision Criteria

We adhered to the national patch test standard, and the dermatologists assessed the skin reaction.

Decision Criteria	Assessment	Grading
No reaction	Negative (−)	0
Slight erythema	Weak positive (±)	0.5
Clear erythema	Positive (+)	1.0
Erythema, swelling and papules	Strong positive (++)	2.0
Erythema, swelling, papules and vesicles	Strong positive (+++)	3.0
Major blister	Strong positive (++++)	4.0

6.3 Analysis

We have calculated the skin stimulation index, and the dermatologists assessed the level of irritation.

Skin stimulation index	Category
Less than or equal to 5.0	Safe product
5.0 ~ 15.0	Permissible product
15.0 ~ 30.0	Improvement required
Equal to or over 30.0	Hazardous product

Skin stimulation index= (The sum of the highest scores for each test subject 24 hours after application, gauged 30 minutes after the removal of the test sample/the number of test subjects) ×100

7 References

1) Chapter 4: Human Patch Test, *Cosmetics, Under the Counter Drugs Manufacturing and Sales Guidebook 2011-12.*
2) Volume 3: Human Patch Test, Chapter 1: Skin Irritation Test, *How to conduct Skin Irritation and Sensitivity Testing as well as How to Evaluate and Measure the Skin Property*
3) Taro Kawamura., Shouji Sasagawa., Tsutomu Masuda., and others. (1970). Basic Research on the Standardisation of Application Tests. *Nippi Kaishi*, 80, p. 301-314.
4) Tetsuro Sugai. (1977). Investigation of Safety of Ointment and Cream on Skin. *Hifu*, 19, P. 102-108.

8 Cancellation Criteria

None of the test subjects qualified for the following cancellation criteria during the test.

When the safety of the test subjects is being jeopardised
When a serious side effect is triggered and the test can no longer be continued
When the doctor deems the test subjects require discontinuing the test

9 Adverse Effects

The test subjects that had the testing sample applied did not admit any adverse effects. However, the erythema that appeared only within the patch test area was not acknowledged as an adverse effect for this particular test.

10 Code of Ethics Examination

This test was carried out in deference to an ethical principle based on the Helsinki Declaration.

11 Testing Agency

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12 Test Results

We have conducted a patch test on a total of 20 test subjects (Male 7, Female 13).
None of the subjects voided during the test period. The total of the test results of the 20 test subjects is indicated below.
The individual Evaluation Chart of the 20 subjects will be illustrated in the appendix in the next chapter.

Background of the Test Subjects

Gender	Number	Average Age
Male	7	29.0±4.2
Female	13	35.7±9.7

Mean ± standard deviation

Total of Evaluation Results

Be・vernal

Decision Criteria	Evaluation after 24 hrs	Evaluation after 48 hrs
Negative (–)	20	20
Weak positive (±)	0	0
Positive (+)	0	0
Strong positive (++)	0	0
Strong positive (+++)	0	0
Strong positive (++++)	0	0

Skin Stimulation Index of Be・vernal was 0.0 and it was categorised as a "Safe product" in the assessment.

Dermatology Specialist Tadashi Shimokata
(Tadashi Shimokata M.D.)

Appendix: Evaluation Chart for Be・vernal

Subject Number	Gender	Age	Evaluation after 24 hours	Evaluation after 48 hours
1	Male	29	(−)	(−)
2	Female	24	(−)	(−)
3	Female	45	(−)	(−)
4	Male	30	(−)	(−)
5	Female	31	(−)	(−)
6	Male	23	(−)	(−)
7	Female	34	(−)	(−)
8	Female	57	(−)	(−)
9	Female	28	(−)	(−)
10	Female	38	(−)	(−)
11	Female	40	(−)	(−)
12	Male	29	(−)	(−)
13	Female	30	(−)	(−)
14	Female	25	(−)	(−)
15	Female	28	(−)	(−)
16	Male	27	(−)	(−)
17	Female	47	(−)	(−)
18	Male	37	(−)	(−)
19	Male	28	(−)	(−)
20	Female	37	(−)	(−)

Testing Agency

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