

## Lyrall<sup>®</sup> has been included in the patch test standard series in Germany

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Lyrall<sup>®</sup> 5% pet. was tested in 3245 consecutive patch test patients in 20 departments of dermatology in order (i) to check the diagnostic quality of this patch test preparation, (ii) to examine concomitant reactions to Lyrall and fragrance mix (FM), and (iii) to assess the frequency of contact allergy to Lyrall in an unselected patch test population of German dermatological clinics. 62 patients reacted to Lyrall, i.e. 1.9%. One third of the positive reactions were ++ and ++++. The reaction index was 0.27. Thus, the test preparation can be regarded a good diagnostic tool. Lyrall and fragrance mix (FM) were tested in parallel in 3185 patients. Of these, 300 (9.4%) reacted to FM, and 59 (1.9%) to Lyrall. In 40 patients, positive reactions to both occurred, which is 13.3% of those reacting to FM, and 67.8% of those reacting to Lyrall. So the concordance of positive test reactions to Lyrall and FM was only slight. Based on these results, the German Contact Dermatitis Research Group (DKG) decided to add Lyrall 5% pet. to the standard series.

**Key words:** 4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde; CAS-No. 31906-04-4; fragrance allergy; fragrance mix; Lyrall<sup>®</sup>; multicentre study; patch test standard series; patch test quality. © Blackwell Munksgaard, 2002.

*Accepted for publication 1 March 2002*

Lyrall<sup>®</sup> (4-(4-hydroxy-4-methylpentyl)-3-cyclohexene-1-carboxaldehyde; CAS-No. 31906-04-4) (International Flavors & Fragrances (IFF), Hazlet, NJ, USA), a synthetic fragrance manufactured and marketed for more than 30 years, has recently gained allergological interest (1–5). Used in scented consumer products, especially in deodorants, Lyrall has not infrequently been reported to cause contact

sensitization. In a large European study, 50 out of 1855 consecutive patients (2.7%) tested with a screening series for fragrance allergy had a positive reaction to Lyrall 5% pet. (5). The German Contact Dermatitis Research Group (DKG) decided to patch test Lyrall 5% pet. in order (i) to confirm the diagnostic quality of the recommended patch test preparation, (ii) to examine concomitant reactions to Lyrall and fragrance mix (FM), and (iii) to assess the frequency of contact allergy to Lyrall in an unselected patch test population of German dermatological clinics.

### Materials and Methods

From March 2000 to February 2001, Lyrall 5% pet. was patch tested in 3245 consecutive patients in addition to the standard series in 20 departments of dermatology, all of them members of the DKG and of the Information Network of Departments of Dermatology (IVDK) (6; <http://www.ivdk.gwdg.de>). The MOAHLFA-Index (7) describing this study population was as follows:

\*Centres of the IVDK contributing to this analysis (in alphabetical order): Aachen (H. Dickel, S. Erdmann), Berlin Charité (T. Zuberbier), Dortmund (P. J. Frosch, C. Pirker), Duisburg (J. Schaller), Dresden (G. Richter), Essen (U. Hillen), Göttingen (Th. Fuchs, J. Geier), Graz (W. Aberer, B. Kränke), Halle (G. Gaber, D. Lübke), Hamburg (M. Kiehn, R. Weißbecher), Heidelberg (M. Hartmann, U. Jappe), Homburg/Saar (P. Koch), Jena (A. Bauer, W. Wigger-Alberti, M. Kaatz), Kiel (J. Brasch), Lübeck (J. Grabbe), Mainz (D. Becker), München Schwabing (M. Agathos), Osnabrück (S. M. John, H. J. Schwanitz, N. Schürer), Rostock (H. Heise), Ulm (H. Gall†, P. Gottlöber and G. Staib).

- Male 39.7%;
- Occupational dermatitis 12.5%;
- Atopic dermatitis 15.5%;
- Hand dermatitis 24.9%;
- Leg dermatitis 11.4%;
- Face dermatitis 13.4%;
- Age of 40 years or more 64.3%.

Patch test exposure time was 24 h in 739 patients (22.8%), and 48 h in 2506 patients (77.2%). Patch tests were performed according to the DKG guidelines (8). Tests were read at least until day 3 (D3), reactions being documented in accordance with the recommendations of the ICDRG with slight amendments by the DKG (8, 9). Allergen preparations were delivered by Hermal (Trolab), Reinbek, Germany. Statistical analysis was made using SAS 8.1. software (SAS Institute, Cary, NC, USA). Only test reactions at D3 were evaluated. Differences in reaction rates in disjunct subgroups of patients were tested for statistical significance using Fisher's exact test. A *p*-value of  $\leq 0.05$  was regarded as significant.

### Results

Of the 3245 patients tested with Lyrall 5% pet., 62 showed a positive test reaction at D3, i.e. 1.9%. 20 of the 62 positive reactions (32%) were ++ and +++. The reaction index according to Brasch & Henseler (10) was 0.27. A detailed description of the patch test results is given in Table 1. In 55 patients with a

Table 1. Patch test results at D3 with Lyrall 5% pet. in 3245 consecutive patients

| Reaction                                                   | <i>n</i> | %     |
|------------------------------------------------------------|----------|-------|
| Negative                                                   | 3147     | 97.0  |
| ? = questionable (erythema only or few follicular papules) | 32       | 1.0   |
| +                                                          | 42       | 1.3   |
| ++                                                         | 17       | 0.5   |
| +++                                                        | 3        | 0.1   |
| Irritant                                                   | 4        | 0.1   |
| Total                                                      | 3245     | 100.0 |

Table 2. Patch test reactions at D3 to Lyrall 5% pet. and fragrance mix 8% pet.

| Lyrall   | Fragrance mix |     |     |    |     |          | Total |
|----------|---------------|-----|-----|----|-----|----------|-------|
|          | Negative      | ?   | +   | ++ | +++ | Irritant |       |
| Negative | 2694          | 134 | 181 | 65 | 8   | 8        | 3090  |
| ?        | 22            | 4   | 4   | 2  |     |          | 32    |
| +        | 10            | 5   | 16  | 7  | 1   |          | 39    |
| ++       | 3             |     | 3   | 8  | 3   |          | 17    |
| +++      | 1             |     |     | 1  | 1   |          | 3     |
| Irritant | 3             |     |     |    |     | 1        | 4     |
| Total    | 2733          | 143 | 204 | 83 | 13  | 9        | 3185  |

positive reaction to Lyrall, data on clinical relevance were given: 27 of these patients (49%) had a history of adverse reactions to perfumes, aftershave, or deodorants. Comparing patients with and without positive reactions to Lyrall by the MOAHLFA-Index, the only significant difference concerned face dermatitis, with 24.2% in Lyrall-positive patients and 13.2% in Lyrall-negative ones ( $p = 0.01$ ). All other items of the MOAHLFA-Index did not differ significantly. The axillae were involved in 3.2% of the patients reacting to Lyrall, but only in 0.6% of those without reaction to Lyrall. This difference reached a borderline significance ( $p = 0.065$ ). The proportion of positive reactions to Lyrall in women was higher than in men (2.2% vs. 1.5%). However, this difference was not statistically significant. Finally, no significant difference in reaction frequencies was seen between patients with 24 h and those with 48 h patch test exposure (1.5% vs. 2.0%).

In 60 patients of the study population (1.8% of 3245), FM was not patch tested. 11 of these patients had a history of fragrance allergy. The individual reasons why the standard series was not tested or why FM was omitted from the standard series in the remaining 49 patients were not evident from the data. Patch test results with Lyrall 5% pet. and FM 8% pet. tested in parallel in 3185 patients are shown in Table 2. Of these patients, 300 (9.4%) reacted to FM and 59 (1.9%) to Lyrall. In 40 of these, positive patch test reactions to both test preparations were observed, which is 13.3% of those reacting to FM and 67.8% of those reacting to Lyrall. Concordance of dichotomized patch test reactions (positive vs. negative/questionable/irritant), as quantified by Cohen's kappa, resulted in a value of 0.20 (95%-confidence interval, 0.14–0.25), indicating only slight agreement.

### Discussion

The patch test preparation Lyrall 5% pet. clearly is a good diagnostic tool: The reaction index of 0.27 indicates a fairly good capability to distinguish between allergic and irritant patch test reactions. In this regard, Lyrall 5% pet. is as good as other standard allergens, e.g. potassium dichromate or cobalt chloride (11). 42 of the 62 positive reactions (68%) were +, which is also comparable to other well-established patch test preparations. Clinical relevance (in terms of fragrance intolerance) was found in 49% of the positive reactions (27/55), a rather satisfying proportion. To date, it has been somewhat difficult to assess the clinical relevance of a positive test reaction to one distinct fragrance, because only 'fragrance' or 'parfum' must be declared on the container of cosmetic products, and no individual substances are listed. The Scientific

Committee on Cosmetic Products and Non-Food Products intended for Consumers (SCCNFP) is of the opinion that consumers should be informed about the known presence in cosmetic products of fragrance ingredients with a well-recognized sensitizing potential. In their 'opinion concerning fragrance allergy in consumers', Lyrall is on the list of those 13 fragrance chemicals with a well-recognized allergenic potential (12). If these fragrances are declared on the container of the cosmetic product in the future, the results of patch tests with individual fragrances will enable patients to avoid their allergen selectively, which at present is only possible by choosing unscented products.

The concordance of positive test reactions to Lyrall and FM was only slight. While about 68% of patients allergic to Lyrall reacted to FM, only 13% of patients allergic to FM reacted to Lyrall. This is in accordance with the results of the European study mentioned above. There, 24 out of 50 Lyrall-positive patients (48%) reacted to FM, and these 24 accounted for 12% of the 198 FM-positive patients (5). Neither test therefore is a good marker for the other. In order not to miss relevant fragrance allergies, Lyrall should be tested in addition to the FM.

In our study, the reaction frequency to Lyrall was 1.9% when tested as a part of a special allergen monitor series in addition to the standard series in consecutive patients. This is considerably, although not statistically significantly, less than the 2.7% positive reactions found in the European multicentre study (5). However, a closer look at the results of that study shows marked differences between the 6 participating centres, ranging from 1.2% in London to 17.0% in Leuven. This probably does not reflect geographical differences in exposure but rather a different selection of patients referred for patch testing. The only German participant in that study observed 1.4% positive reactions, which corresponds quite well to the proportion of 1.9% positive reactions found by us. Therefore, the sensitization rate in German clinical patch test patients is likely to be in that range.

Based on these results, the DKG has decided to add Lyrall 5% pet. to the standard series.

## References

1. De Groot A C. Contact allergy to cosmetics: causative ingredients. *Contact Dermatitis* 1987; 17: 26–34.
2. Handley J, Burrows D. Allergic contact dermatitis from the synthetic fragrances Lyrall and acetyl cedrene in separate underarm deodorant preparations. *Contact Dermatitis* 1994; 31: 288–290.
3. Frosch P J, Pilz B, Andersen K E, Burrows D et al. Patch testing with fragrances. Results of a multicenter study of the European Environmental and Contact Dermatitis Research Group with 48 frequently used constituents of perfumes. *Contact Dermatitis* 1995; 33: 333–342.
4. Hendriks S A, Bousema M T, van Ginkel C J W. Allergic contact dermatitis from the fragrance ingredient Lyrall in underarm deodorant. *Contact Dermatitis* 1999; 41: 119.
5. Frosch P J, Johansen J D, Menné T, Rastogi S C et al. Lyrall® is an important sensitizer in patients sensitive to fragrances. *Br J Dermatol* 1999; 141: 1076–1083.
6. Uter W, Schnuch A, Geier J, Frosch P J. Epidemiology of contact dermatitis. The Information Network of Departments of Dermatology (IVDK) in Germany. *European J Dermatol* 1998; 8: 36–40.
7. Schnuch A, Geier J, Uter W, Frosch P J et al. National rates and regional differences in sensitization to allergens of the standard series. Population-adjusted frequencies of sensitization (PAFS) in 40,000 patients from a multicenter study (IVDK). *Contact Dermatitis* 1997; 37: 200–209.
8. Schnuch A, Aberer W, Agathos M et al. für die Deutsche Kontaktallergie-Gruppe. Leitlinien der Deutschen Dermatologischen Gesellschaft (DDG) zur Durchführung des Epikutantests mit Kontaktallergenen. *Hautarzt* 2001; 52: 864–866.
9. Brehler R, Hellweg B. Beurteilung von Epikutantestreaktionen nach Empfehlungen der Deutschen Kontaktallergie-Gruppe. *Dtsch Dermatol* 1995; 43: 688–690.
10. Brasch J, Henseler T. The reaction index. A parameter to assess the quality of patch test preparations. *Contact Dermatitis* 1992; 27: 203–204.
11. Brasch J, Geier J, Henseler T. Evaluation of patch test results by use of the reaction index. An analysis of data recorded by the 'Information Network of Departments of Dermatology (IVDK)'. *Contact Dermatitis* 1995; 33: 375–380.
12. The Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers (SCCNFP). Opinion concerning fragrance allergy in consumers. A review of the problem. Analysis of the need for appropriate consumer information and identification of consumer allergens. ([http://www.europa.eu.int/comm/food/fs/sc/sccp/out98\\_en.pdf](http://www.europa.eu.int/comm/food/fs/sc/sccp/out98_en.pdf)). Adopted by the SCCNFP during the plenary session of 8 December, 1999. Doc. no. SCCNFP/0017/98 final 1999.

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