

OTC MEDICINES SECTION

ASSESSMENT OF NEW TOPICAL EXCIPIENT

Polyglyceryl-6 polyricinoleate

This is an assessment of a new topical excipient polyglyceryl-6 polyricinoleate (hexaglyceryl monoricinoleate) submitted by [REDACTED] on behalf of [REDACTED]. This excipient is present on the ARTG as a PRV AAN.

The applicant has stated that polyglyceryl-6 polyricinoleate has been used in ‘comparable products’¹ for at least 2 years in USA, Canada, The Netherlands or the UK. The applicant also stated that ‘there are currently no adverse effects known’ (for products containing polyglyceryl-6 polyricinoleate).

The sponsor did not initially provide any toxicity study but has provided an MSDS and a review by the Cosmetic Ingredient Review (CIR) Expert Panel², both for a related compound, glyceryl monoricinoleate which is the monoester of glycerol and ricinoleic acid (castor oil contains 87-90% ricinoleic acid or glycerol ricinoleate) whereas polyglyceryl-6 ricinoleate (polyglyceryl-6 polyricinoleate is polymer of this substance) is the ester of polyglycerin-6 and ricinoleic acid. Recently (June 2007), additional data were provided to address issues that arose during an initial assessment.

According to the MSDS, the toxicological properties of glyceryl ricinoleate have not been ‘thoroughly’ investigated but the MSDS stated that the compound is possibly toxic via oral, inhalation or absorption, and that the signs and symptoms of exposure may include moderate to severe erythema and moderate oedema of the skin.

According to the CIR Expert Panel review, glyceryl ricinoleate is of low acute oral toxicity in mice and rats. In mice, the oral LD₅₀ was >25 mL/kg while in rats, a product containing 5.6% glyceryl ricinoleate had an oral LD₅₀ of >15 g/kg. In skin irritation studies in rabbits³, glyceryl ricinoleate was either a mild irritant or a non-irritant. Similarly, products containing 5.6% glyceryl ricinoleate were either mild irritants or a non-irritant in rabbit studies.

In humans, repeat-insult patch tests have not been conducted with polyglyceryl-6 ricinoleate or glyceryl ricinoleate. However, in single-insult occlusive patch tests conducted in humans, no indication of skin irritation potential was observed for two products (each containing 5.6% glyceryl ricinoleate).

The CIR Expert Panel noted that there were several reported instances of lipstick dermatitis, and castor oil and ricinoleic acid have been implicated in clinical patch test studies on patients experiencing dermatitis, and occasional facial oedema, from use of lipsticks. The review pointed out that castor beans, the source of castor oil from which ricinoleic acid is isolated, contain a toxic polypeptide, ricin, at a concentration of ~3%. Clinical cases of castor bean skin allergy and asthma have been associated with ricin or ‘a protein component’, not with the ricinoleic acid component of the castor bean.

¹ The sponsor’s product is [REDACTED].

² Final report on the safety assessment of glyceryl ricinoleate. Journal of the American College of Toxicology. 7 (6): 721-739 (1988).

³ 24 hour contact, occlusive patch; intact as well as abraded skin.

The CIR Expert Panel concluded that the available data are insufficient to support the safety of glyceryl ricinoleate as used in cosmetics (products contain up to 50% of glyceryl ricinoleate). The Panel required further data including a 28-day chronic dermal toxicity study in guinea pigs, and clinical sensitisation and photosensitisation studies (or an appropriate UV spectrum instead of the photosensitisation data), but the Panel stated that ‘there has been no response or indication of intent to supply’ the required data. Please note that the CIR Review was conducted in 1988, and hence it is not clear whether further studies are available now to address the deficiency in the database for glyceryl ricinoleate.

As with glyceryl ricinoleate, the initial data provided are insufficient to assess the safety of polyglyceryl-6 polyricinoleate.

Further information/data for a related substance (RIPT on polyglyceryl-10 polyricinoleate) has been provided (June 2007) for evaluation, as well as a RIPT for a formulated product containing polyglyceryl-6 polyricinoleate at 0.495% and an expert report on polyglyceryl-6 polyricinoleate.

The RIPT was conducted using polyglyceryl-10 polyricinoleate and was carried out by AMA Labs. Inc (AMA Labs Inc, USA; ref no. MS05.RIPT.K79870.50.BPC; Oct. 2005; E. Dubenskaya) using an initial panel of 52 subjects. The substance tested was Decaglyn PR-20, which was identified as polyglyceryl-10 polyricinoleate in a HTML document (located on internet) on polyglyceryl fatty acid esters. Testing involved preliminary cleaning of application sites. A volume of 0.2 mL of the test material was dispensed onto an occlusive, hypoallergenic patch which was applied directly to the skin of the infrascapular regions of the back. After 24 hours exposure the patch was removed by the subject at home and adverse effects noted. This procedure was repeated for a total of 9 applications over a period of 3 weeks (induction phase). During this period skin reactions were mapped and measured; if a subject observed a reaction is reported to the investigators. Following the induction phase the subject were given a 10-14 days treatment-free period prior to the challenge phase. At challenge, the test patches were applied in a similar manner to that described for the induction phase, with one difference where the challenge application site was a virgin area of skin. Skin reactions were scored at 24 and 48 hours after application, with results based on a comparison between the challenge and induction scores. It was apparent that there were no adverse reactions of any kind recorded during the course of the induction and challenge phases. The material tested in this study was declared to be non-irritant and non-sensitising under the conditions described above. A total of 50 subjects completed the study; two subjects withdrew prior to completion, but both these subjects had not shown any signs of skin reactions during the portion (2-7 treatments) of the induction phase they completed.

A RIPT study on a formulated product containing polyglyceryl-6 polyricinoleate was presented for evaluation (Orentreich Research Corp.; August 2006; Predictive patch test study; Clinique Labs. Inc.). This RIPT was conducted using a panel of 600 subjects with a product identified as Facial Lotion +SPF (MT#2228987); this product (stated by sponsor) is also marketed as City Block Sheer SPF25 (code ID MT#2228987). Ingredients of interest in this formulation are sodium DNA (0.1%), polyglyceryl-6 polyricinoleate (0.5%), trioctyl dodecyl citrate (12%) and ascorbyl tocopheryl maleate (0.0025%). The study involved the use of a modified patch test (Draize), with the test material applied to the upper back of the subjects. The test material was impregnated into a half-inch square gauze patch (had occlusive backing), which was placed on the test site for 48 hours. The application site was

examined for signs of reactivity on removal of the patch. A latent period (to check for delayed reactions) of up to 2 hours was allowed to pass prior to application of the new patch; this sequence was repeated a total of 10 times to constitute the induction period. After a 2 weeks treatment-free period, a challenge patch was applied in a similar to that used during the induction process. A rechallenge was included in the protocol, which took place one week after the first challenge. Assessment of the skin looked for primary skin irritation, skin fatiguing or allergic eczematous contact dermatitis sensitising potential.

Results for each subject were presented, which showed a limited number of occasions at which the subject was not available for assessment of possible skin reactions. There were no reported (recorded) signs of skin damage in any subject during both the induction and challenge phases of this study. It was concluded that the test formulation did not cause skin irritation and it was not a skin sensitiser.

An expert report was provided addressing the dermal safety of polyglyceryl-6 polyricinoleate. The expert stated that there is adequate safety information for polyglyceryl-6 polyricinoleate from both topical application and from oral exposure in foods. The expert cited the attached (described above) RIPT for polyglyceryl-6 polyricinoleate (100%) and noted that it was not a skin irritant or sensitiser. The expert noted that numerous publications have indicated no adverse effects in animals and humans when examined following oral exposure. Kinetic information on polyglyceryl-6 polyricinoleate indicated extensive digestion of the polymer took place in the intestinal tract, excretions of the polyglycerols unchanged and extensive absorption of polyricinoleic (castor oil). There was no evidence of tissue storage of polyglyceryl-6 polyricinoleate or its polymeric components. A description of a 3 generation reproductive toxicity study noted there were no adverse effects in rats fed a diet containing up to 1.5% polyglyceryl-6 polyricinoleate. In chronic toxicity/carcinogenicity studies in rats and mice, no adverse effects were observed at dietary levels of 5% polyglyceryl-6 polyricinoleate delivered over a period of 80 weeks. In a clinical study, no adverse effects on clinical chemistry parameters were observed in 19 humans fed up to 10 g polyglyceryl-6 polyricinoleate per day for 2 weeks. The information cited in the expert report was verified by searching the Food and Chemical Toxicology Journal (36, 1998).

Recommendation

A CIR Expert Panel's review on a related compound, glyceryl ricinoleate, concluded that there is no adequate data to determine if the compound was either safe or not safe. Since polyglyceryl-6 polyricinoleate is related chemically to glyceryl ricinoleate, and since no data have been submitted for polyglyceryl-6 polyricinoleate by the sponsor, the safety of polyglyceryl-6 polyricinoleate can not be based on this information. However, recently submitted data (RIPT on formulated product with polyglyceryl-6 polyricinoleate and on related substance [*polyglyceryl-10-polyricinoleate*], and information of oral toxicity in expert report) indicates that polyglyceryl-6 polyricinoleate is not likely to be a skin irritant or skin sensitiser and it has a low potential for toxicity via the oral route in animals and humans.

Polyglyceryl-6 polyricinoleate is suitable for use as an excipient in OTC products subject to the following conditions:

1. Polyglyceryl-6 polyricinoleate is for dermal use only;
2. The concentration of polyglyceryl-6 polyricinoleate is not to exceed 1%;

3. Polyglyceryl-6 polyricinoleate is not to be included in topical products intended for use in the eye.



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