NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
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This notification is a referral under Article 31 of Directive 2001/83/EC to the CHMP made by The Netherlands:

Product Name in the Referring Member State	Rifadin, suspensie 20 mg/ml
Active substance	Rifampicin
Pharmaceutical form	Oral suspension / Syrup
Strength	20 mg/ml
Route(of Administration	Oral
Marketing Authorisation Holder in the referring Member State	Sanofi B.V.

Background

Rifampicin is a semisynthetic antibiotic with bactericidal activity against mycobacteria, as well as against several other gram-positive and gram-negative organisms.

Rifampicin is indicated for Tuberculosis (TB) and Leprosy, caused by mycobacteria sensitive to rifampicin but also other acute infections caused by rifampicin-sensitive organisms and Brucella infections.
Rifampicin is available in the EU/EEA in different pharmaceutical forms and strengths, such as capsules 150 mg and 300 mg, oral suspension 20 mg/ml (Rifadin), granules for suspension 100 mg/5ml and powder for solution for infusion 600 mg, as well as in combination with isoniazid (Rifinah 300/150 mg film-coated tablets).

Rifadin (rifampicin) oral suspension 20 mg/ml is authorised nationally in Austria, France, Ireland, Italy, Netherlands, Portugal, Spain and Sweden and is used mainly in the paediatric patient population. This oral suspension contains diethanolamine (DEA), an excipient used for stabilisation of the suspension and as pH adjuster.

In 2013, the International Agency for Research on Cancer (IARC) concluded that there is sufficient evidence that DEA and coconut oil diethanolamine condensate (coconut oil DEA) are carcinogenic in animals and classified these as possibly carcinogenic to humans (group 2B). In addition, it cannot be excluded that, when ingested, DEA under specific conditions, such as low pH in the stomach, can be converted to the known genotoxic carcinogen N-nitrosodiethanolamine (NDELA) in the presence of nitrosating agents nitrate/nitrite, potentially from food.

The CHMP Safety Working Party (SWP) calculated a dermal Permitted Daily Exposure (PDE) for DEA of 53 µg/day in the case of lifetime treatment. In the case of a shorter application

period up to 12 months, 705 µg/day could be regarded as the dermal PDE for DEA..[1] However, the SWP PDE would not directly apply to oral administration of DEA-containing medicinal products due to the higher bioavailability of DEA by the oral compared to the dermal route.

On 19 July 2018, the CVMP determined a human oral PDE for DEA of 20 µg/day as part of a review under Article 30(3) of Regulation (EC) No 726/2004. [2]

On 2 May 2019, the CMDh sent a letter to all marketing authorisation holders (MAHs) of products containing DEA and coconut oil DEA as excipients, due to the safety concerns in relation to carcinogenicity. The MAHs were requested to provide a risk assessment regarding the use of diethanolamine and coconut oil DEA. Reformulation of the medicinal product was requested, or a justification why DEA cannot be replaced by another excipient (including a risk mitigation strategy) was to be submitted. Furthermore, MAHs were requested to provide information regarding the potential contamination, and formation of nitrosamines, in view of possible interactions between DEA and present nitrite.

Issues to be considered

The estimated ingested dose of DEA in Rifadin oral suspension is 12 or 24 mg/day, depending on the indication. This is much higher than the dermal PDE of 705 µg/day for exposures < 1 year (or 53 µg/day for lifetime exposure) determined by the SWP, and the oral PDE of 20 µg/day (for lifetime exposure) in humans determined by the CVMP. Therefore, a risk for carcinogenicity cannot be excluded.

Given the above, the MAH concerned by the present Article 31 referral committed to replace DEA from the drug product formula of Rifadin oral suspension. In the corresponding worksharing procedure NL/H/xxxx/WS/382, the Netherlands as Reference Authority concluded on a deadline of Q3 2023 to submit a variation for the new (DEA-free). formulation. To date no reformulation has been proposed. Instead, the MAH proposed to restrict the use of Rifadin suspension. However, a restriction of the indication would not solve the underlying formulation problem since the treated patients would still be exposed to the possibly carcinogenic excipient DEA, in levels far above what would be permitted under the currently available information on the PDE (with 24 mg DEA /day, this would result in 1200 times above the CVMP PDE).

Therefore, the Netherlands considers that the impact of the possibly carcinogenic risk posed by the excipient DEA on the benefit-risk balance of Rifadin oral suspension in its authorised indications should be re-evaluated.

In addition, the Netherlands considers that all possible options to replace DEA have not been sufficiently investigated and that DEA can and should be removed from the drug product formula.

In view of the above and the necessity to take an action at EU level, the Netherlands considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it gives

[1] https://www.ema.europa.eu/en/documents/other/chmp-swp-opinion-diethanolamine-and-coconut-oil-diethanolamine-condensate-excipients_en.pdf

[2] https://www.ema.europa.eu/en/documents/report/cvmp-assessment-report-regarding-request-opinion-under-article-303-regulation-ec-no-7262004-relation-potential-risk-consumer-resulting-use-diethanolamine-excipient_en.pdf

its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

Signed: Priscilla Schoondermark (CMDh-member) Date: 3 June 2026

References:

1. CVMP Assessment Report Regarding the Request for an Opinion under Article 30(3) of Regulation (EC) No. 726/2004 in Relation to the Potential Risk for the Consumer Resulting from the Use of Diethanolamine as an Excipient in Veterinary Medicinal Products for Foodproducing Species. 2018, www.ema.europa.eu/en/documents/report/cvmp-assessment-report-regarding-request-opinion-under-article-303-regulation-ec-no-7262004-relation-potential-risk-consumer-resulting-use-diethanolamine-excipient_en.pdf .

2. Opinion of the SWP Regarding Diethanolamine and Coconut Oil Diethanolamine Condensate as Excipients. 2021, www.ema.europa.eu/en/documents/other/chmp-swp-opinion-diethanolamine-and-coconut-oil-diethanolamine-condensate-excipients_en.pdf.