25 April 2018
EMA/CVMP/243810/2018
Committee for Medicinal Products for Veterinary Use

European public MRL assessment report (EPMAR)

Solvent naphtha, light aromatic (all food producing species)

On 28 March 2018 the European Commission adopted a Regulation[1] establishing maximum residue limits for solvent naphtha, light aromatic in all food producing species, valid throughout the European Union. These maximum residue limits were based on the favourable opinion and the assessment report adopted by the Committee for Medicinal Products for Veterinary Use.

Solvent naphtha, light aromatic is intended for use in all food producing species as an excipient in a formulation for cutaneous use.

Zoetis Belgium SA submitted to the European Medicines Agency an application for the establishment of maximum residue limits on 02 October 2015.

Based on the original and complementary data in the dossier, the Committee for Medicinal Products for Veterinary Use recommended on 5 October 2017 the establishment of maximum residue limits for solvent naphtha, light aromatic in all food producing species.

Subsequently the Commission recommended, on 6 February 2018, that maximum residue limits in all food producing species are established. This recommendation was confirmed on 27 February 2018 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 28 March 2018.

[1] Commission Implementing Regulation (EU) No 2018/520, O.J. L 87, of 02 April 2018

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Summary of the scientific discussion for the establishment of MRLs

Substance name:	Solvent naphtha, light aromatic
Therapeutic class:	NO ENTRY
Procedure number:	EMEA/V/MRL/004321/FULL/0001
Applicant:	Zoetis Belgium SA
Target species:	All food producing species
Intended therapeutic indication:	Not applicable (for use as an excipient)
Route(s) of administration:	Cutaneous use (pour-on)

1. Introduction

Solvent naphtha, light aromatic (CAS No. 64742-95-6) is a mixture of light aromatic hydrocarbons from refined petroleum distillates, with an aromatic content of 98% or greater. It is composed primarily of C9-10 dialkyl and trialkylbenzenes. It contains approximately 46% trimethylbenzenes, 36% ethylmethylbenzenes, 0 to 5% xylene, 0 to 5% cumene, and 1.5% ethylbenzene; the exact composition and concentrations vary.

Solvent naphtha, light aromatic is used as an excipient in a pour-on formulation for cattle at a dose of 15 µl/kg. The substance is intended for use in all food producing species.

Although mineral hydrocarbons have a 'No MRL required' classification, aromatic and unsaturated compounds are excluded from this provision due to potential genotoxic and/or carcinogenic risks from substances containing polycyclic aromatic hydrocarbons (CVMP summary report EMEA/CVMP/069/95-FINAL and Regulation (EU) No 37/2010).

2. Scientific risk assessment

2.1. Safety assessment

2.1.1. Overview of pharmacological properties

Pharmacodynamic properties including mode of action

As solvent naphtha, light aromatic will be used as an excipient in veterinary medicinal products it has no intended pharmacodynamic effect. However, solvent naphtha, light aromatic may have pharmacological effects, including at doses lower than those eliciting toxicological effects. In particular, based on published results of cognitive neurobehavioral testing in rats exposed by inhalation (0, 200, 1000, and 5000 mg/m^3 for 8 hours/day for 3 consecutive days), a pharmacological inhalation NOEC of 200 mg/m^3 was derived for solvent naphtha, light aromatic. This corresponds to an oral NOEL of 76 mg/kg bw according to ECHA conversion equation[2] using a standard breathing volume of 0.38 m^3/kg bw for 8-hour exposure under the assumption of total absorption.

Pharmacokinetic properties (mainly in laboratory animals)

[2] ECHA Guidance on information requirements and chemical safety assessment, Chapter R.8 https://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf/e153243a-03f0-44c5-8808-88af66223258

No data or references on the pharmacokinetic characteristics of the components of solvent naphtha, light aromatic were provided.

The pharmacokinetic properties of mineral hydrocarbons are briefly discussed in the existing CVMP Summary Report (EMEA/CVMP/069/95-FINAL). The rate of absorption of linear alkanes (n-alkanes) and branched alkanes from the gut has been shown to become lower as the carbon number increases, n-alkanes of carbon numbers higher than 29 are not significantly absorbed. Although not extensively studied, the smallest of the cyclic alkanes are considered to be rapidly taken up by the gut. Dermally applied mineral hydrocarbons with carbon numbers higher than 10 do not appear to cross the full thickness of the skin and enter the blood circulation.

After distribution via lymph nodes and the liver absorbed hydrocarbons are further distributed to adipose tissues. As larger molecules are not readily absorbed and smaller molecules are more readily mobilised for metabolism to fatty acids by the liver (and further metabolism to normal components of the body or carbon dioxide), medium sized hydrocarbons (C20 to C30) are the main substances which accumulate in animal and human tissues.

Branched and cyclic alkanes are less efficiently oxidised than n-alkanes.

No pharmacokinetic data in laboratory species have been provided for solvent naphtha, light aromatic. This is accepted, as generation of such data is not considered feasible due to the inherent complexity of the material.

2.1.2. Calculation of pharmacological ADI, if relevant

Based on the oral NOEL of 76 mg/kg bw derived from the neurobehavioral inhalation study in rats, a pharmacological ADI of 0.76 mg/kg bw was calculated.

2.1.3. Overview of toxicology

Single-dose toxicity

No acute dose toxicity studies were provided. This is acceptable as such studies are considered to be of low relevance for the establishment of MRLs.

Repeated dose toxicity

A study report of a 90-day repeated oral dose toxicity study in rat was provided. The GLP status of this study is unknown. Following dosing of 0, 30, 125, 500 and 1250 mg/kg bw/day solvent naphtha, light aromatic for 5 days per week clinical signs (including salivation, pale reddish brown oral discharge and perineal staining) were observed at doses of 500 mg/kg bw/day and above, and a reduction in body weight gain and in body weight were observed at doses of 500 and above and 1250 mg/kg bw/day, respectively. Target organs were the liver and the kidney. Liver cell hypertrophy was observed in both sexes at doses of 500 mg/kg bw/day and above, accompanied by increased alanine aminotransferase and total protein, and increased bilirubin at 1250 mg/kg bw/day in males, and by increased alanine aminotransferase and total protein at 1250 mg/kg bw/day in females. Increased relative liver weight was observed at 1250 mg/kg bw/day in males and at 500 mg/kg bw/day and above in females. In males a dose-related increase in severity of hyaline droplets and cortical tubular degeneration without a dose-response relationship were observed. These findings were not correlated with effects on clinical chemistry or organ weight. In females a significant increase in relative kidney weight at 500 mg/kg bw/day and above was accompanied by increased alkaline phosphatase at 1250 mg/kg bw/day. Since

solvent naphtha, light aromatic was only administered 5 days/week, an adjusted NOAEL value of 89 mg/kg bw/day corresponding to 7 days/week treatment was calculated.

The results from a 90-day repeated toxicity study in dogs with oral dosing of solvent naphtha light aromatic (0, 125, 250, or 500 mg/kg bw/day in capsules for at least 90 days) were provided. The study was conducted in accordance with GLP. The NOAEL for this dog study was considered 125 mg/kg bw/day based on borderline anaemia and watery stool in males.

A published 12-month rat chronic repeat dose inhalation toxicity study using a high aromatic naphtha-consisting of a 50/50 blended mixture of two equivalent commercial products was provided. Wistar rats were exposed to 0 (control), 450, 900 or 1800 mg/m^3 of the mixture for 6 hours/day, 5 days/week for up to 12 months. The mixture was analysed by capillary gas chromatography and was reported not to contain cumene. The main findings in the study included increased liver and kidney weights following 1800 mg/m^3 in males which, in the absence of histopathological changes, were considered as physiologically adaptive responses. No treatment-related histopathological abnormalities, including hyperplasia or neoplasia, were found. A NOEC of 900 mg/m^3 was derived, adjusted for the 5 days per week treatment to estimate a 7 day exposure per week, and converted to an equivalent oral NOEL of 109 mg/kg bw/day using a standard breathing volume for 6-hour exposure of 0.17 m^3/kg bw adapted to rats of this body weight and under the assumption of total absorption.

Since cumene was not present in the material used in the above study, the toxicity of cumene was considered separately. Data from a 3-month National Toxicology Program study of cumene in rats by inhalation produced a LOAEL of 62.5 ppm, equivalent to 37.5 mg/kg bw/day, based on increased relative kidney weights seen in males. Using this value a permitted daily exposure (PDE) of 0.75 mg/day was derived for cumene using an uncertainty factor of 2500 (5 for interspecies variation, 10 for intraspecies variation, 5 for duration of treatment, 10 for use of LOAEL). This PDE of 0.75 mg/day is still higher than the PDE of 0.7 mg/day derived from a carcinogenicity study performed with cumene (reported below) and consequently the PDE of 0.7 mg/day can be considered to also be protective for chronic toxicity of cumene.

Reproductive toxicity, including developmental toxicity

In a literature study the reproductive toxicity of solvent naphtha light aromatic was investigated in a 3-generation inhalation study in rats. The GLP-status of the study is not known but the study generally meets the requirements in current guidelines (VICH GL 22, OECD 416). In the first generation (F0), parental animals (30/sex/group) were exposed to 0 (negative control), 100, 500, or 1500 ppm for 6 hours/day, 7 days/week for 10 weeks before mating and for up to 2 weeks of cohabitation. Females were exposed 6 hours/day, 7 days/week from GD0 (gestation day 0, i.e. the day on which mating was confirmed) to GD20. After parturition, exposure for the dams was re-initiated on PND (postnatal day) 5 for 6 hours/day and 7 days/week, and was continued until end of weaning (PND 21) when the dams were euthanized. The second generation litters (F1), culled to 8 (4 /sex), were kept with their dams until end of weaning when 30 F1 pups/sex/group were selected to generate the F2 generation. Exposure to the same concentrations and period as their parents started when the pups of the youngest litter reached PND 28. At weaning (PND 21) of the F2 pups, 40 pups/sex/group were selected to generate the F3 generation and exposed to the same concentrations and periods as their parents but with an earlier start, i.e. from PND 22.

Overall there were no consistent effects on reproductive performance, i.e. a reproductive NOAEC-value of 1500 ppm, equivalent to approximately 7362 mg/m^3 and an oral NOAEL of approximately 2135 mg/kg bw/day. The conversion to an oral NOAEL was performed using equations established by ECHA (2012)[1] using a standard breathing volume of 0.29 m^3/kg for 6 hours for adult rats, and in case of pups corrected

with an allometric factor of 1.6 to take into account the low body weight of the pups. Significant maternal toxicity (maternal deaths and significantly reduced body weight gain) was reported for the high dose group in each generation and consequently no NOAEC could be established. For pup toxicity an oral NOAEL of 227 mg/kg bw/day was calculated from a NOAEC of 100 ppm based on deaths observed among the 22-day old pups in the F2 generation (exposed from PND 22) and decreased weight gain observed in the mid-and high-dose groups across all generations.

In an oral developmental study, solvent naphtha light aromatic was given to pregnant rats at dose levels of 0 (vehicle control), 125, 625 and 1250 mg/kg bw/day (24 rats per group) from GD 6 to GD 15. This is a GLP-study consistent with the requirements in current guidelines (VICH GL 32, OECD 414). Animals were observed from GD 0 and during treatment and sacrificed on GD 20 for gross post mortem evaluation and microdissection of foetuses. The results indicated maternal toxicity in terms of lower weights, weight gain and food consumption from 625 mg/kg bw/day, decreased foetal weight and increased incidences of foetuses with ossification variations at 1250 mg/kg bw/day. No teratogenic effects were evident from external, visceral or skeletal evaluations. A NOAEL of 125 mg/kg bw/day was derived for maternal toxicity, a NOAEL of 625 mg/kg bw/day was derived for foetal toxicity and a NOAEL of 1250 mg/kg bw/day (highest dose tested) were derived for teratogenicity.

In a public literature study pregnant CD-1 mice (30 per group) were exposed by inhalation to solvent naphtha light aromatic at concentrations of 0, 100, 500, or 1500 ppm for 6 hours/day from GD 6 to GD 15 (McKee et al., 1990). Exposures to 1500 ppm caused maternal deaths in nearly half of the animals and resulted in fetal mortality, greatly reduced fetal body weights, delayed ossification, and an increased incidence of cleft palate in the litters of the surviving dams. Exposure to 500 ppm caused a smaller, but significant, reduction in maternal body weight gain and reduced mean fetal body weights, but there were no structural malformations. The lowest concentration of 100 ppm caused no maternal or developmental toxicity. Based on these results, the NOAEC for both maternal toxicity and fetal toxicity in mice was 100 ppm (approximately 490 mg/m^3) corresponding to 245 mg/kg bw/day according to ECHA equation and using a breathing volume of 0.5 m^3/kg bw; the NOAEC for teratogenicity (based on cleft palate at 1500 ppm, a dose that also caused maternal deaths) was 500 ppm (approximately 2454 mg/m^3 corresponding to 1227 mg/kg bw/day).

Genotoxicity

Solvent naphtha, light aromatic was tested for genotoxicity using the standard battery of tests including an *in vitro* bacterial reverse mutagenicity assay, an *in vitro* test for chromosomal effects in mammalian cells (human peripheral lymphocytes) and an *in vivo* test for chromosomal effects using rodent hematopoietic cells.

Negative results were reported in both *in vitro* tests. However, the results of the *in vitro* test for chromosomal effects were not consistent with those obtained in a similar study reported in the literature. The discrepancy between the results of these two studies may be related to the high degree of cytotoxicity (approximately 80% as measured as decrease in mitotic index) induced by solvent naphtha, light aromatic in the published study, which is likely to have caused positive responses.

Negative results were also reported in the *in vivo* peripheral blood micronucleus assay after oral administration for 3-days. Although this study was performed in rats using CD71-positive reticulocytes in peripheral blood in accordance with OECD Guideline 474, which is considered acceptable, the positive controls were below the historical range and not acceptable according to the guideline OECD 474. Consequently the test is considered invalid. A new *in vivo* bone marrow micronucleus test in male rats on solvent naphtha, light aromatic (219.6, 439.2, and 878.4 mg/kg bw/day) was conducted in accordance

with the OECD 474 guideline. The test substance was concluded to be negative for the induction of micronucleated polychromatic erythrocytes in this test system.

Overall, the totality of evidence including the negative results of *in vitro* and *in vivo* genotoxicity testing suggests that solvent naphtha, light aromatic is devoid of genotoxic potential.

Carcinogenicity

No carcinogenicity study was provided.

The 90-day oral administration studies with solvent naphtha, light aromatic in rats and dogs did not reveal pre-neoplastic changes such as hyperplasia and nor did the 12-month study reported in the literature investigating the chronic toxicity of a high aromatic naphtha-consisting of a 50/50 blended mixture of two equivalent commercial products. However, as noted above, the test material used in the 12-month study did not include cumene.

A PDE of 0.7 mg/day for cumene was estimated by the FDA based on a LOEL of 169 mg/kg/day in a mouse carcinogenicity study in which increased incidences of alveolar/bronchiolar neoplasms were observed in males and females at all dose levels and using an uncertainty factor of in total 12000 (12 to account for extrapolation from mice to humans, 10 to account for differences between individuals, 1 for duration of treatment, 10 because of oncogenic effects were reported and 10 because a NOEL was not established).

Solvent naphtha is classified under the CLP (Classification Labelling and Packaging) regulation (EC) No 1272/2008 as presumed to have carcinogenic and mutagenic potential for humans when benzene is present at concentrations above 0.1%. Benzene is in itself classified as carcinogenic and mutagenic and is mentioned in the VICH GL 18 (guideline on impurities: residual solvents) as a solvent that should be avoided and controlled at or below 2 ppm.

Studies of other effects including immunotoxicity and neurotoxicity

A subchronic neurotoxicity study in rats from the public literature was referred to. Adult male Sprague Dawley rats were exposed by inhalation to 0, 100, 500, and 1500 ppm solvent naphtha light aromatic for 6 hours/day and 5 days/week during 90 days and tested for motor activity and in a functional observation battery (Douglas et al., 1993). The GLP-status of the study is not known but the study appears to generally meet the requirements in current guidelines (OECD 424). However, only male rats were included. No neurobehavioral effects or histopathological changes in nervous tissues. The NOAEC for neurotoxicity was 1500 ppm corresponding to 7500 mg/m^3. As this is higher than the pharmacological NOEC of 200 mg/m^3, which was based on acute neurotoxic effects, and the NOAECs obtained for repeated dose toxicity studies (1800 mg/m^3) and reproductive toxicity studies (490 mg/m^3), the NOAEC in the subchronic neurotoxicity study will not have any influence on the toxicological ADI or the overall ADI.

No indications of immunogenic effects were seen in the available repeated dose toxicity studies and consequently no immunotoxicity studies were performed.

2.1.4. Calculation of the toxicological ADI or alternative limit

The oral NOAEL from the chronic toxicity study in rats was 109 mg/kg bw/day, which would result in an ADI of 1.09 mg/kg bw/day, applying an uncertainty factor of 100. However, the test material used in the study did not contain cumene. A PDE for cumene has been set at 0.7 mg/day, or 0.012 mg/kg bw/day based on a mouse carcinogenicity study that can be used as a reference value.

2.1.5. Overview of microbiological properties of residues

Solvent naphtha, light aromatic is not classified as an antimicrobial agent and is not structurally related to antimicrobial agents used in human or animal medicine. Data on microbiological properties are therefore not considered necessary.

2.1.6. Calculation of microbiological ADI

As solvent naphtha, light aromatic is not expected to possess antimicrobial activity the establishment of a microbiological ADI is not relevant.

2.1.7. Observations in humans

No data on effects of solvent naphtha, light aromatic in humans were available.

2.1.8. Findings of EU or international scientific bodies

Solvent naphtha, light aromatic has not been evaluated for use in medicinal products by EU or international scientific bodies. However, it has been classified under the CLP (Classification Labelling Packaging) regulation EC No 1272/2008 as presumed to have carcinogenic and mutagenic potential for humans when benzene is present at concentrations above 0.1%.

2.1.9. Overall conclusions on the ADI

A pharmacological ADI of 0.76 mg/kg bw (45.6 mg per person) was set by applying an uncertainty factor of 100 to the oral NOEL of 76 mg/kg bw/day derived from the acute inhalation neurobehavioral study.

A toxicological ADI of 1.09 mg/kg bw/day (65.4 mg per person) was set by applying an uncertainty factor of 100 to the oral NOAEL of 109 mg/kg bw/day from the chronic toxicity study in rats.

Derivation of a microbiological ADI was not considered necessary for solvent naphtha, light aromatic.

As the pharmacological ADI is lower than the toxicological ADI, the pharmacological ADI is established as the overall ADI.

In addition, a separate toxicological reference value was established for cumene (which may be present in solvent naphtha, light aromatic) as the toxicity of cumene is not adequately covered by the pharmacological ADI (toxic effect of cumene may not be evident in the types of pharmacology studies performed) or the toxicological ADI (the study from which the ADI was derived used test material that did not contain cumene). The established PDE of 0.7 mg/kg bw/day (42 mg per person/day) represents an appropriate toxicological reference value for cumene.

The establishment of a microbiological ADI is not considered necessary.

2.2. Residues assessment

No data or references on the metabolism and residue kinetics or depletion of residues of solvent naphtha, light aromatic or its components were provided.

The conclusion of the CVMP summary report on mineral hydrocarbons (EMEA/CVMP/069/95-FINAL) that the total intake of mineral oils from all veterinary sources (including ingredients in parasiticides) is sufficiently low that the health of consumers will not be affected by any residues resulting from their use

in veterinary medicine is not applicable to solvent naphtha, light aromatic as the report for mineral hydrocarbons does not take aromatic hydrocarbons into account.

2.2.1. Pharmacokinetics in target species

No pharmacokinetic data in laboratory species have been provided for solvent naphtha, light aromatic. This is accepted as generation of such data is not considered feasible due to the inherent complexity of the material.

2.2.2. Residue depletion studies

No residue depletion studies are available. Worst case exposure calculations have been provided (see 3.3).

Selection of marker residue and ratio of marker to total residues

No marker residue or ratio of marker to total residues is proposed as a “No MRL required” classification is recommended.

2.2.3. Monitoring or exposure data

No monitoring or exposure data were available.

2.2.4. Analytical method for monitoring of residues

No analytical method was provided as a “No MRL required” classification is proposed.

2.2.5. Findings of EU or international scientific bodies

Solvent naphtha, light aromatic has not been evaluated by EU or international scientific bodies.

3. Risk management considerations

3.1. Potential effects on the microorganisms used for industrial food processing

As the substance is not expected to possess antimicrobial activity no effects on microorganisms used for industrial food processing are expected.

3.2. Other relevant risk management considerations for the establishment of maximum residue limits

Restrictions to the cumene and benzene content of solvent naphtha are necessary in order to protect consumer health. A limit for cumene of 2.5% would lead to a consumer exposure below the PDE based on a conservative worst case calculation with the existing product which takes into account the consumption of meat and milk. For benzene the limit of 0,0002%, i.e. 2 ppm, as recommended in VICH GL 18 will ensure consumer exposure in compliance with the TTC concept (i.e. consumer exposure is expected to remain below 0.15 µg/day) under this worst case scenario.

A restriction to the cutaneous route of application is recommended as limited oral administration data were available for evaluation and as solvent naphtha, light aromatic is used in a pour-on formulation. A

restriction on the dose of solvent naphtha to be administered to the target animal is also necessary in order to ensure that the worst case consumer exposure estimate is applicable for all products containing solvent naphtha, light aromatic .

3.3. Elaboration of MRLs

A conservative “worst case” estimate of consumer exposure to solvent naphtha, light aromatic and its components that would occur as a result of ingestion of 500 g meat and 1.5 litres milk from animals treated with the existing pour-on product for cattle is 0.44 mg/kg bw/day (26.4 mg/day). This is below the ADI of 45.6 mg/day. The worst case estimate assumes application of a maximum dose of 15 µl/kg bw to the target animal and uniform distribution. The worst case exposure estimate for cumene is 0.011 mg/kg bw/day
(0.66 mg/day), which is below the selected toxicological reference value of 0.7 mg/day recommended in ICH Q3C. The worst case exposure estimate for benzene is 0.88 ng/kg bw/day (0.0528 µg/person per day), which is below the threshold of toxicological concern for carcinogenicity of 0.0025 µg/kg bw/day (0.15 µg/person per day).

It should be noted that the assumptions used to estimate the worst case exposure were conservative, including 100% dermal absorption, no volatility and no metabolism/excretion. The actual level of intake of residues is expected to be well below the worst case estimate and consequently a “No MRL required” classification is recommended for all food producing species.

3.4. Considerations on possible extrapolation of MRLs

Not applicable as the recommendation is for all food producing species.

3.5. Conclusions and recommendation for the establishment of maximum residue limits

Having considered that:

- solvent naphtha, light aromatic is intended for use as an excipient in products for cutaneous application,
- an ADI of 45.6 mg/day was established for solvent naphtha, light aromatic; as this value does not consider toxicity that might arise due to cumene in solvent naphtha, light aromatic, a separate toxicological reference value (PDE) of 0.7 mg/day has been established for cumene,
- a worst case consumer estimate indicates that consumer exposure to residues of solvent naphtha, light aromatic will remain at safe levels,
- a limit for benzene of 0.0002%, a limit for cumene of 2,5%, a limit of 15 µl solvent naphtha/kg bw of the animal, and a restriction to cutaneous application are considered necessary in order to ensure that worst case consumer exposure estimate remains valid for all veterinary medicinal products containing solvent naphtha, light aromatic,

The Committee concludes that the establishment of maximum residue limits for solvent naphtha, light aromatic is not necessary for the protection of human health, and therefore recommends the inclusion of solvent naphtha, light aromatic in table 1 of the Annex to Regulation (EU) No 37/2010 as follows:

Pharmacologically active substance	**Marker residue**	**Animal species**	**MRLs**	**Target tissues**	**Other provisions**	**Therapeutic classification**
Solvent naphtha, light aromatic, with cumene concentration not exceeding 2.5 %, and benzene concentration not exceeding 0.0002 %.	NOT APPLICABLE	All food producing species	No MRL required	NOT APPLICABLE	For cutaneous use only. Only at volume not exceeding 15 µl solvent naphtha/kg bw.	NO ENTRY

4. Background information on the procedure

Submission of the dossier	2 October 2015
Steps taken for assessment of the substance	
Application validated:	21 October 2015
Clock started:	22 October 2015
List of questions adopted:	18 February 2016
Consolidated responses to list of questions submitted:	13 March 2017
Clock restarted:	14 March 2017
List of outstanding issues adopted:	12 May 2017
Oral explanation:	6 September 2017
Clock restarted:	6 September 2017
CVMP opinion adopted:	5 October 2017