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Information for the package leaflet regarding ethanol used as an excipient in medicinal products for human use

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This document should be read in the context of the revision of the Annex of the European Commission guideline 'Excipients in the labelling and package leaflet of medicinal products for human use' (EMA/CHMP/302620/2017) [3].

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Information for the package leaflet regarding ethanol used as an excipient in medicinal products for human use

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Executive summary

This document has been written in the context of the revision of the Annex of the European Commission Guideline on 'Excipients in the label and package leaflet of medicinal products for human use' (EMA/CHMP/302620/2017 [3], SANTE-2017-11668 [32].

Ethanol (alcohol) serves many purposes in medicines. For example, it can be a solvent, preservative, or cutaneous penetration enhancer.

Although, ethanol can impair cognitive and psychomotor functions, exposure to ethanol when used as an excipient in medicines is usually limited. Dose volumes and concentrations usually result in exposures far less than drinking alcoholic beverages, although some effects on performance are possible.

Although exposure is usually low, it is important to note that the effect of long-term exposure to even low levels of ethanol in medicines on the health and development of children has not been evaluated. Excessive alcoholic beverage consumption during pregnancy can result in foetal alcohol syndrome (FAS) which can include learning and behavioural problems. This raises concern that there is at least, in theory, a risk to development from chronic exposure to ethanol during childhood. In neonates elevated levels of the metabolite acetaldehyde have been observed after exposure to ethanol from medicines. Although the clinical significance is unclear, this observation is a concern.

In neonates, cutaneous absorption of ethanol is significant, and this may lead to significant local reactions (e.g. haemorrhagic skin necrosis) and systemic toxicity. This contrasts with older children and adults where even excessive cutaneous exposure to ethanol, results in only minor increases in systemic levels.

The main reason for updating the information in the package leaflet is the potential effects in children.

1 # Updated information in the package leaflet

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Ethanol	Oral, parenteral, inhalation	Zero	This medicine contains x mg of alcohol (ethanol) in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>><(y% w/<w><v>)>. The amount in <dose><volume> of this medicine is equivalent to less than A ml beer or B ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.	Where ethanol is present as a processing agent (for example in tablet coating) or extraction solvent and is evaporated off (under the level of ICH Q3C) there is no need to mention ethanol in patient information. To calculate the equivalent volume of beer and wine, assume the ethanol content of beer to be 5% v/v (alcohol by volume, ABV), which is equivalent to 4% w/v, and of wine to be 12.5% v/v or 10% w/v (the specific gravity of ethanol has been approximated as 0.8). Volumes of beer and wine (A and B) should be rounded up to the next whole number.
		15 mg/kg per dose	This medicine contains x mg of alcohol (ethanol) in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>><(y% w/<w><v>)>. The amount in <dose><volume> of this medicine is equivalent to A ml beer or B ml wine. The amount of alcohol in this medicine is not likely to have an effect in adults and adolescents, and its effects in children are not likely to be noticeable. It may have some effects in younger children, for example feeling sleepy.	To calculate the equivalent volume of beer and wine, assume the ethanol content of beer to be 5% v/v (alcohol by volume, ABV), which is equivalent to 4% w/v, and of wine to be 12.5% v/v or 10% w/v (the specific gravity of ethanol has been approximated as 0.8). Where relevant, the interactions of ethanol should be stated in the SmPC (section 4.5). ***Suggestion for information in the SmPC:*** A dose of (select maximum dose) of this

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
			The alcohol in this medicine may alter the effects of other medicines. Talk to your doctor or pharmacist if you are taking other medicines. If you are pregnant or breast-feeding, talk to your doctor or pharmacist before taking this medicine. If you are addicted to alcohol, talk to your doctor or pharmacist before taking this medicine.	medicine administered to (a child A years of age and weighing B kg or an adult weighing 70 kg) would result in exposure to C mg/kg of ethanol which may cause a rise in blood alcohol concentration (BAC) of about D mg/100 ml (see Appendix 1 of report EMA/CHMP/43486/2018). For comparison, for an adult drinking a glass of wine or 500 ml of beer, the BAC is likely to be about 50 mg/100 ml. Co-administration with medicines containing e.g. propylene glycol or ethanol may lead to accumulation of ethanol and induce adverse effects, in particular in young children with low or immature metabolic capacity. When a dose is given over prolonged period (e.g. by slow infusion over several hours), the rise in BAC will be less and the effects of ethanol may be reduced. In such cases the package leaflet and SmPC should include a statement such as: Because this medicine is usually given slowly over XX hours, the effects of alcohol may be reduced.
		75 mg/kg per dose	This medicine contains x mg of alcohol (ethanol) in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>> (y% w/<w><v>). The amount in <dose><volume> of this medicine is equivalent to A ml beer or B ml wine. The alcohol in this preparation is likely to affect children. These effects may include feeling sleepy and changes in behaviour. It may also affect their ability to concentrate and take part in physical activities. The amount of alcohol in this medicine can affect your ability to drive or use machines. This is because it may affect your judgement and how fast you react. If you have epilepsy or liver problems, talk to your doctor or pharmacist before taking this medicine. The amount of alcohol in this medicine may alter	

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
			the effects of other medicines. Talk to your doctor or pharmacist if you are taking other medicines. If you are pregnant or breast-feeding, talk to your doctor or pharmacist before taking this medicine. If you are addicted to alcohol, talk to your doctor or pharmacist before taking this medicine.	
	Cutaneous	Zero	This medicine contains x mg alcohol (ethanol) in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>> (y% w/<w><v>). It may cause burning sensation on damaged skin.	In neonates (pre-term and term newborn infants), high concentrations of ethanol may cause severe local reactions and systemic toxicity due to significant absorption through immature skin (especially under occlusion). The corresponding warning in the SmPC/PL should be added if appropriate. Depending on the product and concentration of ethanol, the warning "flammable" may be necessary. Inclusion of warnings on use near an open flame, lit cigarette or some devices (e.g. hairdryers) should be considered.

Scientific background

1. Characteristics

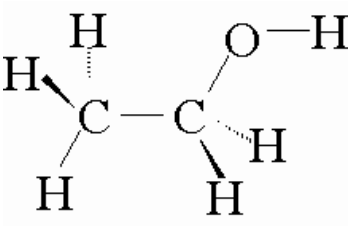
1.1. Category (function)

Ethanol is used as a solvent to dissolve the active ingredient in some medicines or as an extraction solvent in herbal medicinal products. Ethanol has also been used as an antimicrobial preservative, possessing bactericidal and fungicidal activity. Due to its volatility ethanol has been used in the formation of topical films and medicated nail lacquers. Ethanol is a permeation enhancer used in some topical preparations (Martindale [2]). Ethanol may perform other functions in formulations.

1.2. Physico-chemical Properties

Ethanol is also known as alcohol or ethyl alcohol (CH_3CH_2OH or C_2H_6O). Monographs for anhydrous ethanol (not less than 99.5%) and ethanol 96% are given in the European Pharmacopeia. Ethanol is described as a colourless, clear, volatile, flammable, hygroscopic liquid; that burns with a blue, smokeless flame. It has a boiling point of 78°C and is miscible with water and with dichloromethane.

Structure of Ethanol



1.3. Use in medicinal products

Ethanol has been used in oral liquids such as ranitidine, furosemide, phenobarbital, trimethoprim, co-trimoxazole and paracetamol as a solvent or antimicrobial preservative (Marek et al., 2014 [66]; Whittaker et al., 2009 [103]). It is occasionally used as a solvent in parenteral medicines such as paclitaxel and other cytotoxic injections/infusions. It may also be used as a solvent in flavouring agents added to medicines.

Ethanol is used in medicines over a wide range of concentrations. For example, where present as a solvent in the flavouring component in an oral medicine it can be present at less than 0.1 g in 5 ml (2%). In oral liquids where ethanol is present as a preservative, it might be present at about 0.5 g in 5 ml (10% w/v). Less commonly it is present in oral and parenteral medicines at higher concentrations, for example when used as a solvent. Often exposure to ethanol from medicines is low. Exposure can be similar to amounts that might be consumed with foods or just a small volume of beer or wine. Occasionally exposure can be higher, for example an infusion paclitaxel for an adult patient can contain 20 g ethanol equivalent to 1 glass of wine.

Exposure is affected by the dose volume and weight of the patient. Medicines may be taken more than once a day. The table below gives examples of exposures from single doses of medicines. The list based on products that have been marketed; there may be similar products either ethanol-free or containing a different amount of ethanol available. The products listed have high ethanol contents. The list is not exhaustive.

Product	Ethanol content (% age)	Example single dose volume at age & weight (kg)	Ethanol exposure (mg/kg)	Predicted rise in BAC (mg/100 ml)
Glass of wine (included for comparison)	10% w/v	210 ml taken by an adult (70 kg).	300 mg/kg	50 mg/100 ml
Phenobarbital 15 mg/5 ml Elixir	30% w/v 300 mg/ml	If 4 mg/kg given as part of a divided dose (1.33 ml/kg) (dose for children 2-6mg divided in 2 to 3 doses)	400 mg/kg	67 mg/100ml
80 mg lopinavir/ 20 mg of ritonavir oral solution	42.4% v/v 356.3 mg/ml	0.2 ml/kg taken by a 14-day old child (4 kg) would be 0.8 ml.	71 mg/kg	12 mg/100 ml
Furosemide 20 mg/5 ml solution	10% v/v 80 mg/ml	A 1 kg neonate taking a 3 mg/kg dose would take 0.75 ml oral solution.	70 mg/kg	12 mg/100 ml
Paracetamol 120 mg/5 ml elixir	10 % v/v 500 mg/5ml	A 2-month-old baby (5 kg) taking 2.5 ml dose.	50 mg/kg	8 mg/100 ml
Tamoxifen liquid	19% w/v 150 mg/ml	20 ml taken by an adult (70 kg).	43 mg/kg	7 mg/100 ml
Digoxin 50 mcg/ 1 ml Elixir	8% w/v 80 mg/1ml	Part of a divided loading dose 25 mcg/kg (0.5 ml/kg) used for children. Part of a divided maintenance dose 5 mcg/kg (0.1 ml/kg) used for children.	40 mg/kg 8 mg/kg	6.7 mg/100 ml 1.3 mg/100 ml
Ranitidine 75 mg/5 ml oral solution	8% w/v 400 mg/ 5 ml	A 3-year-old (15 kg) taking a single dose 5 mg/kg would take 5 ml.	27 mg/kg	4.5 mg/100 ml
Salicylate / Cetalkonium Teething gel	33.45% w/w 334.5 mg/g	0.5 g of gel applied to the gums of a 1 year old (10 kg).	17 mg/kg	2.8 mg/100 ml
Ritonavir 80 mg/ml oral solution	43.2 % v/v 344 mg/ml	50 mg (0.6 ml) taken by a child 3 years of age (15 kg).	14 mg/kg	2.3 mg/100 ml
Nystatin 100,000 Ul/ml oral suspension	0.8% w/v 8 mg/ml	A 1 ml dose taken by a new born of 2 kg.	4 mg/kg	0.67 mg/100 ml

Codeine phosphate 5 mg/5 ml oral solution	2% v/v 156 mg/10 ml	10 ml taken by a 70 kg adult.	2.2 mg/kg	0.37 mg/100 ml
Metronidazole 200 mg/5 ml oral suspension	0.64% w/v 6.4 mg/ml	A child weighing 8 kg taking a dose of 7.5 mg/kg would take 60 mg or 1.5 ml.	1.2 mg/kg	0.2 mg/100 ml

The table below is similar to the above except it focuses on parenteral medicines. Ethanol can be metabolised at a rate of 0.1 g/kg/hour. When ethanol is given slowly in an infusion it may be metabolised as it is given, which might result in lower BACs than expected.

Product	Ethanol content (% age)	Example single dose volume at age & weight (kg)	Ethanol exposure (mg/kg)	Predicted rise in BAC (mg/100 ml)
Paclitaxel 6 mg/ml concentrate for solution for infusion	39.3% w/v 393 mg/ml	An adult patient (70 kg) with a surface area of 1.8 m^2 receiving a dose of 175 mg/m^2 would receive 315 mg (52.5 ml of the concentrate).	295 mg/kg	50 mg/100 ml Given slowly over 3 hours, so effects reduced.
Etoposide Concentrate for Solution for Infusion, 20 mg/ml	24.1% w/v 241 mg/ml	An adult patient (70 kg) with a surface area of 1.8 m^2 receiving a dose of 150 mg/m^2 would receive 270 mg (13.5 ml of the concentrate).	46.5 mg/kg	8 mg/100 mg Given slowly over 3 hours, so effects reduced.
Phenytoin 50 mg/ml injection	8% w/v 80 mg/ml	A 1 kg neonate receiving a loading dose of 20 mg/kg. Maintenance dose 5 mg/kg.	32 mg/kg 8 mg/kg	5.3 mg/100 ml 1.3 mg/100 ml
Docetaxel 80 mg/2 ml concentrate and solvent for solution for infusion	10% w/v 100 mg/ml	An adult patient (70 kg) with a surface area of 1.8 m^2 receiving a dose of 75 mg/m^2 would receive 135 mg or 1.7 ml of the concentrate.	9.2 mg/kg	1.5 mg/100 ml
Diazepam 5 mg/ml injection PL 01502/0025	25% w/v 250 mg/ml	A 1 month old (4 kg) given 1 mg (0.2 ml).	6.25 mg/kg	1 mg/100 ml

Nimodipine 0.02% Solution for Infusion (10 mg nimodipine in 50 ml)	20% w/v 200 mg/ml	An adult patient being infused 2 mg nimodipine (10 ml) per hour	28 mg/kg/h	4 mg/100 ml Given slowly by continuous infusion so effects reduced

The phasing out of chlorofluorocarbons (CFCs) in inhalers the 1990's and introduction of hydrofluorocarbon (HFA) posed several formulation problems. The solubility of some active ingredients and excipients were reduced in HFA and in some cases, ethanol was introduced as a co-solvent to solubilise the ingredients (Myrdal et al., 2014 [83]). Although inhaled ethanol bypasses first-pass metabolism (MacLean et al., 2017 [62]) and reaches the brain more rapidly than for other routes of administration, the exposure to ethanol from medicinal metered dose inhalers is very low.

The table below gives examples of exposures from doses of inhaled medicines and demonstrates the low ethanol exposure from inhaled medicines. The list based on products that have been marketed; there may be similar products either ethanol-free or containing a different amount of ethanol available. The list is not exhaustive.

Product	Ethanol content (% age)	Example single dose volume at age & weight (kg)	Ethanol exposure (mg/kg)	Predicted rise in BAC (mg/100ml)
Salbutamol inhaler	4 mg ethanol per actuation	A 12-year-old (40 kg) taking two puffs	0.2 mg/kg	0.03 mg/100 ml
Beclomethasone 100 micrograms per actuation inhaler	7.5 mg ethanol per actuation	A 2-year-old (12 kg) taking two puffs	1.25 mg/kg	0.2 mg/100 ml
Ipratropium 20 micrograms per actuation inhaler	8.4 mg ethanol per actuation	A 1-month-old (4 kg) taking 1 puff	2.1 mg/kg	0.35 mg/100 ml
Salmeterol 25 micrograms per actuation inhaler	1.6 mg ethanol per actuation	A 12-year-old (40 kg) inhaling 4 puffs	0.16 mg/kg	0.027 mg/100 ml
Iloprost 10 mcg/ml nebuliser solution	0.81 ethanol mg/ml	A 70 kg adult inhaling 5 mcg or 0.5 ml	0.005 mg/kg	0.0008 mg/100 ml
Glyceryl trinitrate micrograms per metered dose sublingual spray	9.6 mg ethanol /metered dose	An adult spraying two metered doses under the tongue	0.56 mg/kg	0.093 mg/100 ml

Ethanol is used in various cutaneous dosage forms (e.g. sprays, topical solutions and gels) where its properties as a penetration enhancer can be employed. It is also used in topical products such as medicated nail lacquers where it evaporates off leaving an active containing layer. Moreover, it is employed in processes such as the film coating of tablets and in the purification of active substances by crystallisation. In these cases, ethanol is evaporated off with only trace amounts remaining.

Finally, ethanol can be used as an extraction solvent in herbal medicinal products (liquid extracts and tinctures) and in the production of mother tinctures for homoeopathic preparations. Most liquid homeopathic preparations are also formulated in aqueous/alcohol solution according to ethanol concentrations laid down in manufacturing methods described in the European Pharmacopoeia or, in the absence thereof, by the pharmacopoeias currently used officially in the Member States.

2. Pharmaco-toxicological data

2.1. Pharmacodynamic effects

Ethanol is an endogenous substance but can affect numerous physiological systems when exposure is sufficient. Ethanol is a dose-dependent CNS depressant. $GABA_A$ receptors (γ-aminobutyric acid A) have been implicated as a target for the in vivo actions of ethanol contributing to effects such as reduced anxiety, behavioural disinhibition, sleepiness and muscle relaxation. Many other receptors are implicated for example, nicotinic anticholinergic (Ach) receptors, cannabinoid receptors, N-methyl-D-aspartate (NMDA) and non-NMDA receptors including kainate receptor subtypes. Acute alcohol exposure results in an increase in synaptic dopamine and serotonin. Ion channels and intracellular signal cascades are also affected (Brunton et al., 2011 [13]).

The impact of ethanol on the cardiovascular system is complex. Although a mild coronary vasodilatation occurs within hours after ethanol consumption, long-term heavy ethanol use is associated with hypertension (Chan et al., 2014 [16]). Ethanol at high doses can prolong the QT interval and ventricular repolarisation. Chronic alcohol use causes supraventricular tachyarrhythmias, atrial fibrillation, and cardiomyopathy (Chan et al., 2014 [16]). A large proportion of patients with idiopathic cardiomyopathy are alcohol-dependent. An increased incidence of haemorrhagic and ischemic stroke has been attributed to chronic ethanol consumption and cases of stroke following prolonged binge drinking are noted especially in younger adults (Brunton et al., 2011 [13])

Diuresis is another well documented pharmacodynamic effect. Ethanol inhibits the release of vasopressin (antidiuretic hormone) from the posterior pituitary gland, resulting in enhanced diuresis (Chan et al., 2014 [16]).

Ethanol appears to stimulate gastric secretions promoting the release of gastrin and histamine and beverages containing more than 40% alcohol have an adverse local effect on the stomach. High levels of alcoholic beverage consumption are associated with oesophageal reflux and other oesophageal conditions. Heavy consumption can also disrupt the gastric mucosal barrier and cause acute and chronic gastritis. Some alcoholics have chronic diarrhoea caused by structural and functional changes in the small intestine (flattened villi decreased digestive enzymes) resulting in malabsorption (Brunton et al., 2011 [13]) Chronic alcohol use is associated with a number of anaemias. Acute and chronic alcoholic beverage use can lead to impotence in men (Brunton et al., 2011 [13]). However, given the low exposure from ethanol in medicines, many of the effects caused by high exposures are of little relevance.

2.2. Toxicology

In the available pre-clinical literature, a large number of studies that have been undertaken with ethanol, are at doses that are intended to emulate that of recreational alcohol consumption and its role in, for example, the production of alcoholic liver disease (ALD) and foetal alcohol syndrome (FAS) in humans and neonates.

This leads to doses used and exposures achieved that are often several factor fold above those that would be expected through the use of ethanol as a pharmaceutical excipient.

Therefore, in the absence of purpose designed studies with ethanol, at levels comparable to that seen in pharmaceuticals, a degree of extrapolation of findings is required from existing studies (in particular with juvenile studies, where there exists very little literature).

2.2.1. Single dose toxicity

Overall, ethanol has a low order of acute toxicity by all routes of exposure. (EPA, 1995; UNEP, 2005)

Oral

Ethanol has a low order of toxicity in animals following single oral exposure. Robust figures are:

LD_{50}=8300 mg/kg (oral, mouse) (Bartsch, 1976 [6]) and LD_{50}=15010 mg/kg (oral, rat) (Youssef et al. et al., 1992 [109]). An age-related difference is reported (Wiberg et al., 1970 [106]) in which young rats (100 days old) were less sensitive than old rats (10–12 months old) with an LD_{50}=11,000 mg/kg versus 7000 mg/kg.

Inhalation

In acute inhalation studies, ethanol has shown a low order of acute toxicity. An LC_{50} value was not achieved at exposures of up to 60,000 ppm for 60 minutes in a study in CD-1 mice (Moser et al., 1985 [79]). Mice in this study experienced moderate ataxia, which reversed after more than 4 hours recovery period at all exposure levels.

Dermal

No acute dermal toxicity was reported in a study in rabbits, LD_{L0}=20,000 mg/kg (Monick, 1968 [78]) and although this study is not experimentally robust, the result is consistent with the finding that ethanol uptake through intact skin is poor.

2.2.2. Repeat-dose toxicity

Repeat dose toxicity from a dietary study with rats at doses >2400 mg/kg showed in male rats minor changes to organ weights and haematology/biochemistry; female rats showed minor biochemistry changes and increased length of oestrus cycle along with liver nodules (NTP, 1996 [84]); adverse liver effects were observed at concentrations of 3600 mg/kg bw/day and above (Holmberg et al., 1986 [38]).

2.2.3. Genotoxicity

Genotoxic effects described in the literature and reported below are seen at exposure levels well above that expected with the use of ethanol as an excipient in medicines.

Ethanol as an industrial chemical is not classified a genotoxic substance. Ethanol was negative in a bacterial mutagenic test (AMES test) as well as for most of other genotoxic testing reported in the

literature. There is some evidence of sister chromatid exchange (SCE) in vivo and of aneugenic effects at very high doses of ethanol but overall, there is no evidence of a relevant genotoxic hazard for humans (Phillips et al., 2001 [90]).

However, the results of an in vitro study of ethanol using the Cytokinesis Blocked Micronucleus assay (CBMN) indicate that ethanol, and its metabolite acetaldehyde, produce statistically significant dose-dependent increases in micronucleus induction when compared to controls. This study also demonstrated using kinetochore staining that micronucleus induction in ethanol originated from an aneugenic mechanism, whereas for acetaldehyde most of the micronuclei had originated by a clastogenic mechanism. This indicates that ethanol has a genotoxic effect independent of the mechanism of action of acetaldehyde (Kayani et al., 2010 [46]).

The effect of ethanol on in vivo DNA damage was assessed in pregnant mice using single cell gel electrophoresis (Comet) assay. Pregnant mice were orally administered 20 v/v% ethanol (2, 4 or 8 g/kg) on Day 7 of gestation. Additionally, the 4 g/kg group was pre-treated with the acetaldehyde dehydrogenase inhibitor disulfiram, to increase the build-up of acetaldehyde in vivo. The 4 and 8 g/kg ethanol treatments were shown to induce DNA damage in brain, lung and embryos at 4 and 8 hours after treatment. There was no significant increase of DNA damage observed with the disulfiram pre-treated group (4 mg/kg) compared to the 8 g/kg group. These data suggest that ethanol induces DNA damage, and since pre-treatment of disulfiram did not increase DNA damage, the DNA damage observed may not be an effect of acetaldehyde (Kido et al., 2006 [48]).

Concerns regarding the genotoxicity of metabolites of ethanol have been raised. For example, acetaldehyde remains the metabolite of most concern with respect to the genotoxic effects. However, there is uncertainty whether such effects occur following metabolism of ethanol from alcoholic beverages. Given that exposure to ethanol when used as an excipient in medicines is usually lower, concerns in this regard are further reduced (COM/2015/S2 [20]).

2.2.4. Carcinogenicity

Ethanol in alcoholic beverages is classified as carcinogenic to humans (group 1) by the International Agency for Research on Cancer (IARC, 2010 [43]).

This IARC evaluation is based on (i) the epidemiological evidence, which showed little indication that the carcinogenic effects depend on the type of alcoholic beverage, (ii) the sufficient evidence that ethanol causes cancer in experimental animals; and (iii) the mechanistic evidence in humans who are deficient in aldehyde dehydrogenase that acetaldehyde, a potentially genotoxic compound derived from the metabolism of ethanol in alcoholic beverages, contributes to the causation of malignant oesophageal tumours. Identification of ethanol as a known carcinogenic agent in alcoholic beverages does not rule out the possibility that other components may also contribute to their carcinogenicity (IARC, 2010 [43]).

These evaluations are based on chronic consumption of ethanol in alcoholic beverages. For example, female breast cancer is one of the more affected types of cancer and the risk is said to increase by 7% for every additional drink consumed regularly each day (equivalent to about 10 g/day) (IARC, 2010 [43]).

A study in mice demonstrated that long term ethanol consumption leads to intestinal tumour genesis. Animals consumed between 270 mg and 706 mg a day of ethanol in drinking water for 1 year. Exposure was not calculated against the body weight of the animals. The study showed that long term ethanol consumption, without additional carcinogen treatment or prior suppressor gene inactivation, leads to intestinal hyperproliferation, DNA damage and intestinal tumour genesis. It is noted that the

carcinogenic findings seen in this study, when using a conservative estimate of exposure, are seen at exposures well above those expected from the use of ethanol in medicines (Müller et al., 2017 [81]).

It is also noted that numerous animal experiments have been performed with various procarcinogens and carcinogens administered to animals with and without alcohol. The majority of these experiments found that ethanol enhances chemically induced carcinogenesis (WHO, 2010 [104]).

Exposure to ethanol from medicines is usually much lower and not relevant to exposures seen through alcoholic beverage consumption. Therefore, an increased carcinogenic risk would be considered negligible for ethanol as an excipient in medicines.

2.2.5. Reproductive and developmental toxicity

Available literature shows that ethanol can cause adverse development and teratogenic effects in laboratory animals. Developmental alterations were observed consistently in offspring of monkeys with blood levels greater than 1.5 g/l following once a week ethanol administration, initiated at the start of gestation. Infants exposed only after gestation day 40 were less consistently abnormal despite higher blood ethanol levels (5.5 g/l) (IARC, 1988 [42]).

It has been shown that sub-chronic ethanol ingestion in mice produces morphologic gamete anomalies as well as somatic genotoxicity in both males and females administered 10% ethanol for 27 days, with animals receiving 23 g/kg/day and 21.5 g/kg/day respectively. The effects seen in this study were observed at exposures well above those expected through the use of ethanol in medicines (Cebral et al., 2011 [15]).

A study in mice showed that facial and central nervous system defects consistent with foetal alcohol syndrome were induced with alcohol dosages where maternal blood alcohol levels did not exceed 200 mg/dl (Sulik at al., 2005 [98]).

In rats, prenatal exposure to ethanol 20% V/V in diet induced DNA damage in osteoblasts of newborns, as shown by micronucleus formation and higher percentage of DNA in the comet tail (Carvalho et al., 2016 [14]).

Effects in pregnancy are also available (see below section on clinical safety, special populations).

2.2.6. Juvenile animal studies

Numerous toxicity studies in neonatal and/or juvenile animals have been published in mice and rats. Many studies aimed to determine the effect of single or chronic dose ethanol on neurological parameters such as locomotor activity, behaviour, social interaction, tolerance or molecular targets (enzymes, receptors) in different brain regions. Findings were those expected from the known effects of ethanol on the CNS. The juvenile toxicity studies cited in this guidance reports effects in animals exposed to $\geqslant$2500 mg/kg ethanol. Typical exposure from ethanol in medicines is usually much lower than this value (Murawski et al., 2012 [82]; Molet et al., 2012 [77]; Pascual et al., 2012 [89]; Przybycien-Szymanska et al., 2011 [91]; Broadwater et al., 2011 [11]).

3. Pharmacokinetics (in humans)

3.1. Absorption, distribution, metabolism and elimination

Absorption

Ethanol is absorbed from the stomach (20%) and intestines (80%) by simple diffusion. Ethanol absorption is largely dependent on gastric emptying rates because it is more rapidly absorbed in the duodenum. Peak levels can occur 30-60 minutes after ingestion (Marek et al., 2014 [66]; Norberg et al., 2003 [86]). Food in the stomach delaying gastric emptying can decrease the rate of absorption (Chan et al., 2014 [16]).

Distribution

Following absorption ethanol readily distributes into tissues and body fluid, crossing the blood–brain and placental barriers. Ethanol does not exhibit any protein binding; it's volume of distribution is dependent on water content. In adults, total body water content is approximately 45% to 60% of total body weight (Marek et al., 2014 [66]). Neonates and children may have a larger water compartment than adolescents and adults. Water content has been reported to decrease from 92% in premature new-borns to 75% in full-term new-borns and then to 60% by age 1 (Lamminpää et al., 1995 [54]).

Metabolism

About 95–98% of ingested ethanol is metabolised (Norberg et al., 2003 [86]). Ethanol can be metabolised by oxidative pathways to acetaldehyde by alcohol dehydrogenase (ADH), microsomal ethanol-oxidising system (MEOS), or catalase. A small fraction of ethanol is metabolised by alternative non-oxidative pathways (Geertinger et al., 1982 [28]).

Ethanol is metabolised by oxidative means as follows: ethanol →acetaldehyde →acetate →acetyl-coenzyme A which feeds into the Krebs cycle and is ultimately broken down into carbon dioxide and water.

Metabolites of ethanol such as acetaldehyde have toxic effects. Acetaldehyde is a highly reactive molecule and has been linked to longer term effects such as alcoholic liver disease. It is also associated with nausea, vomiting, facial flushing (vasodilation) reduced psychomotor function, muscle weakness, and hypotension in adults consuming excessive amounts of ethanol (Gorgus et al., 2016 [30]).

Alcohol metabolic rates show interindividual and ethnic variability. The best-known genetic polymorphism in ALDH genes is in ALDH2 affecting about half of the East Asian population (including the Han Chinese, Taiwanese, and Japanese). Individuals who are heterozygous or homozygous show accumulation of acetaldehyde and the characteristic sensitivity reaction (facial flushing, increased skin temperature and heart rate), following alcohol intake (Ramchandani et al., 2013 [93]).

Elevated acetaldehyde blood levels were also noted in a study in neonates being regularly dosed with oral liquid preparations containing ethanol (iron and furosemide) (Pandya et al., 2016 [88]) (see 4.2 Safety in special populations).

Elimination

Small amounts of ethanol are excreted unchanged in breath, sweat and urine: accounting for less than 10% of ethanol elimination. Ethanol is mainly eliminated by metabolism. Only at low levels where the BAC is less than approximately 15 mg/100 ml is the elimination rate dose-dependent, undergoing first-order elimination (Marek et al., 2014 [66]). At higher doses, enzymes become saturated and the

elimination of ethanol becomes a zero-order process. In adults the elimination rate of ethanol is approximately 0.10 g/kg/h regardless of sex (Norberg et al., 2003 [86]).

In neonates and young infants ADH activity may be fraction of that of an adult, although other enzymes are thought to play a role. It has been suggested that even though neonates have a around one-tenth the ADH concentrations of an adult, catalase concentrations may be equivalent to or higher than adults (Hon, 2018 [40]; Tran et al., 2007 [99]). Elimination rates in preterm newborn infants have been reported to be less than or equivalent to adults 0.06–0.11 g/kg/h (Ford et al., 2013 [27]) (adult elimination rate ~0.1 g/kg/h) (Norberg et al., 2003 [86]). Rates one third to twice that of their mothers have also been reported for term newborn infants (Lamminpää et al., 1995 [54]). Generalisations on elimination are difficult due to individual variability but case reports of infants between 1 and 3 months of age showed elimination rates comparable to those of adults while a 7-month-old showed elimination twice as fast as the average for adults (Lamminpää et al., 1995 [54]). In children 1.5–13 years elimination of ethanol up to twice as fast as the average for adults has been reported (~0.2 g/kg/h) (Ford et al., 2013 [27]). Elimination in 14-year-old adolescents is similar to adults (Lamminpää et al., 1994 [53]).

3.2. Interactions

Ethanol may interact with other drugs or excipients in the following ways:

- pharmacodynamic interactions
- pharmacokinetic interactions
- effects on absorption

Pharmacodynamic interactions

Ethanol is a CNS depressant and the most commonly reported interaction is sedation. Drugs that can cause CNS depression, such as antihistamines, anxiolytics, hypnotics, opioids, and antidepressants may therefore potentiate the effects of ethanol and vice versa (Stockley's Drug Interactions, Chan et al., 2014 [16]).

Drug interactions potentially exist between ethanol and medicines affecting cardiac conductance, such as tricyclic antidepressants and sodium channel antagonists; as well as therapies for treating high blood pressure e.g. calcium channel blockers. Interactions with ethanol (high exposures 800mg ethanol/kg) and anti-hypertensive calcium channel blockers have been noted. For example light-headedness and increase in heart rate have been reported with felodipine and nifedipine (Chan et al., 2014 [16]).

Pharmacokinetic interactions

Substances that inhibit or compete for the enzymes ADH or CYP2E1 might interact with ethanol. For example, the metabolite of verapamil, norverapamil, is partially metabolised by CYP2E1. Significantly higher BACs were noted in subjects regularly taking verapamil. Accumulation of norverapamil has also been attributed to ethanol likely through competition for CYP2E1 (Chan et al., 2014 [16]). Abacavir used in the treatment of HIV infection is metabolised primarily by oxidation by ADH and glucuronidation. Reasonably high exposures to ethanol (700 mg/kg) appeared to increase AUC, Cmax and half-life of abacavir (Chan et al., 2014 [16]).

A further concern for young children is the potential interaction between substances competing for the same, perhaps immature, metabolic pathway, e.g. ethanol and propylene glycol. Adverse events were seen when Kaletra, an oral solution containing both ethanol and propylene glycol was administered to neonates. It is possible that ethanol and propylene glycol are metabolised by similar metabolic

pathways. It was considered that ethanol may have competitively inhibited the metabolism of propylene glycol leading to accumulation of propylene glycol and associated toxicity. Exposure was approximately 80 mg/kg ethanol and 187 mg/kg propylene glycol. Most of the 10 infants affected were premature, receiving their first dose on the day or the day after birth. Onset of toxicity occurred within 1 to 6 days in most of the cases although this was delayed to 20 days in one full-term infant. The delay in toxicity was attributed to the accumulation of propylene glycol (FDA Drug Safety Communication: Serious health problems [24]).

Disulfram is a drug which has been used as a deterrent, along with other supportive treatments, in patients with drinking problems. It is a prodrug and its metabolites inhibit the metabolism of acetaldehyde by blocking aldehyde dehydrogenase (ALDH). When ethanol is ingested it is metabolised to acetaldehyde and then to acetic acid by ALDH. When ALDH is blocked by the disulfram-metabolites, acetaldehyde accumulates causing unpleasant effects such as peripheral vasodilatation, flushing, pulsating headache, tachycardia, nausea, and dizziness. More severe reactions are also possible requiring medical intervention (Martindale [2]; Chan et al., 2014 [16]). Other drugs may interact with ALDH causing disulfiram-like symptoms. These include metronidazole, nitrofurantoin, some cephalosporin antibiotics (e.g. cefoperazone, cefotetan and cefuroxime), chloramphenicol, first generation sulfonylureas (e.g. chlorpropamide), and some antifungals (e.g. griseofulvin) (Chan et al., 2014 [16]). A mild disulfiram reaction is said to occur in some disulfram-patients who apply alcohol to the skin (Stockely's Drug Interactions). A reaction following ingestion of an ethanol-containing cough mixture has been reported in a patient taking disulfiram (Koff et al., 1971 [51]).

Effects on the absorption

The potential for rapid release or "dose dumping" of certain sustained release opioid formulations caused by the co-administration of alcoholic beverages has been noted. Although the modified release mechanism for most formulations are unaffected by the presence of ethanol, the dissolution of one marketed product was found significantly affected by alcohol and the product suspended on safety grounds (EMA/355008/2011 [4]; EMA Scientific Guidelines, Quality of medicines questions and answers: Part 2 [22]).

Ethanol can affect absorption in other ways; for example, alcoholic beverage consumption (270 mg ethanol/kg) appeared to increase the absorption of tetracycline by about a third (Chan et al., 2014 [16]).

4. Clinical safety data

4.1. Safety in adult patients

Despite widespread recreational use of ethanol in adults there remain many unknowns especially with regard to low-level ethanol-exposure when present as an excipient in medicines.

Ethanol is present as an endogenous substance that can be detected in the blood of man, at levels around 0.03 mg/100 ml (range 0–0.15 mg/100 ml) (Jones et al., 1983 [45]; Logan et al., 2000 [60]; Watanabe-Suzuki et al., 1999 [102]). Endogenous ethanol is produced from metabolism (from acetaldehyde via reversible ADH reactions) and by carbohydrate fermentation in the intestinal tract by gut flora (Geertinger et al., 1982 [28]).

Ethanol is present in a number of food stuffs, such as fruit, bread and yogurt. A number of investigators have measured the ethanol content of fruit juices. The amounts of ethanol in a 200-ml glass of fruit juice may vary from almost nothing to over 100 mg (Gorgus et al., 2016 [30];

Kiesewetter et al., 1996 [49]; Lund et al., 1981 [61]; Honma et al., 1985 [41]; Wucherpfennig , 1982 [108]). The below table summarises the findings in regard to alcohol in fruit juices.

Author	Drink	mg ethanol/l or ppm	mg in 200 ml
Lund (1981) [61]	Orange juice	5–800 Mean Fresh 590 Mean Canned 460	1–160 118 92
	Grapefruit Juice	70–520 Mean Fresh 220 Mean Canned 246	14–104 44 49
Wucherpfennig (1982) [108]	Various fruit drinks	100–1000	20–200
Honma (1985) [41]	Apple juice	52.5–740	10–148
	Orange Juice	7.5–767.5	1.5–153
	Grapefruit Juice	235–1610	57–322
	Grape Juice	130–660	26–132
	Lemon juice	565–1140	113–228
Kieswetter (1996) [49]	Various fruit juices	106–890	21–178
	Grapefruit juice	840–1610	168–322

It has been estimated that the diet of a 6 year old would result in exposure to ethanol from food of 10.3 mg/kg/day but this may fluctuate and higher exposures 12.5–23.3 mg/kg/day may occur (Gorgus et al., 2016 [30]). The dietary ethanol exposure of young children with milk-based diets is unknown.

In adults' effects have been noted at BAC levels as low as 15 mg/100 ml where the ability to perform complex psychomotor tasks during the rapid absorption phase have been noted (Modell et al., 1990 [76]). Impairments in cognitive function and reaction times have been documented at BACs of 30 mg/100 ml (Breitmeier et al., 2007 [9]). BACs of 15 mg/100 ml to 30 mg/100 ml might result from an adult drinking around 60–120 ml wine.

The thresholds for warning statements in the package information take into consideration when the effects of ethanol may become apparent and gives three threshold levels for ethanol exposure as shown in the table below:

Threshold for warning statements in the package leaflet	**Rationale for warning statements in the package leaflet** The appropriateness of ethanol in a formulation is determined considering risk versus benefit. These thresholds refer the levels above which a warning is required (see Information in the package leaflet).
Zero (to less than 15	Some medicines contain a very small amount of ethanol. At these levels it would not be expected to have any noticeable effect.

mg/kg/dose)	This lower band covers ethanol exposure up to the equivalent of adult drinking 10 ml of wine (15 mg/kg) which might result in a Blood Alcohol Concentration (BAC) of 2.5 mg/100 ml. A similar exposure would occur if 5 ml of medicine containing 100 mg ethanol, (introduced with the flavouring agent) were given to a 7-kg child (15 mg ethanol/kg/dose). It should be noted that elevated levels of the metabolite acetaldehyde were seen in neonates exposed to levels of ethanol in this lower band (median (range) 7.24 (2.27–78.42) mg ethanol/dose) (Pandya et al., 2016 [88]).
15 to less than 75 mg/kg/dose	This middle band covers ethanol exposures equivalent to an adult drinking 10–50 ml wine. Adolescents and adults would not be expected to notice significantly the effects of ethanol at these levels. If these amounts are scaled down based on weight then, children are also unlikely to notice the effects of ethanol at these levels although less certainty exists particularly with respect to young children. A warning in the package leaflet, in respect to affects in young children only, is given at these levels.
Equal to or above 75 mg/kg/dose	75 mg/kg dose of ethanol would produce a BAC of 12.5 mg/100 ml. For a 70-kg adult a 75 mg/kg dose of ethanol would be approximately 5,250 mg (5.25 g) of ethanol which is equivalent to approximately 50 ml of wine. Reduced psychomotor abilities have been noted above similar levels (15 mg/100 ml) (Modell et al., 1990 [76]; Breitmeier et al., 2007 [9]). Occasionally and where justified, it may be necessary to use ethanol in medicines in amounts that would exceed 75 mg/kg/dose. Warnings regarding the effects of ethanol are required when ethanol exposure exceeds these levels. Only rarely does exposure from medicines reach levels similar to drinking alcoholic beverages. Exposure equivalent to an adult drinking 1 glass of wine (300 mg/kg) could result in a BAC of 50 mg/100 ml which is similar to the limit for driving in many EU countries.

Ethanol intake, typically from recreational use, of 0.3 g/kg to 1.8 g/kg (equivalent to 1 to 6 glasses of wine) might result in BAC 50–300 mg/100 ml. BAC concentrations up to 180 mg/100 ml may result in changes is vision, reaction time, coordination and emotional lability. Higher BAC concentrations 180 to 350 mg/100 ml may cause loss of judgement, slurred speech, diplopia, blurred vision, ataxia, blackouts, sweating, tachycardia, nausea, vomiting and incontinence (Martindale [2]).

Very high intakes (in excess of 1.8 g/kg resulting in BAC more than 300 mg/100 ml) can cause stupor, coma, hypothermia, respiratory depression and cardiovascular toxicities such as atrial tachycardia, AV block and hypotension (Martindale [2]). Lethal doses of ethanol are said to occur at in adults at 5–8 g/kg (Litovitz, 1986 [58]).

Alcohol consumption is associated with physical injury. At the low exposure levels from medicines risk of injury is limited provided precautions are observed e.g. in relation to driving or operating machinery. Other disease outcomes are also influenced by alcohol consumption. Research focuses on alcoholic beverage consumption rather than the lower exposures, sometimes short-term use, when used as a

pharmaceutical excipient. Effects of exposure to low levels alcoholic beverages provide some information relevant to medicines. For example, although consumption of alcoholic beverages can cause a fall in blood sugar and make diabetic patients more likely to experience hypoglycaemia; however, moderate ethanol consumption is associated with a reduced risk of type 2 diabetes (Rehm et al., 2010 [96]).

Hypertension is increased by the consumption of alcoholic beverages; a slight increase in blood pressure was found in men reporting as few as 1 to 2 drinks per day, however, moderate consumption has been found to be protective for women in some studies (Marchi et al., 2014 [65]). Chronic heavy drinking has been associated with adverse cardiac outcomes; however, light to moderate regular consumption has been linked to reduced risk and severity of ischaemic coronary events. Positive effects were achieved with 12 g ethanol (1 drink) every other day, with no benefits for more than 20 g per day. Heavy alcohol consumption is associated with increased risk of dysrhythmias. The association became significant in persons consuming more than 36 g ethanol per day although the risk of atrial fibrillation reoccurring at lower levels has been noted. An exponential relationship between alcohol consumption and the risk of haemorrhagic stroke has been found, however, low to moderate alcohol consumption (1–2 drinks per day) seemed to have a protective effect on ischaemic stroke, with increases risk occurring at higher levels of consumption (Rehm et al., 2010 [96]).

Pancreatitis is associated with alcohol consumption. Risks associated with the consumption of two or fewer drinks (< 24 g) were comparable to non-drinkers. Alcoholic beverage consumption has a detrimental effect on the skin-condition psoriasis. A dose-response relationship has been proposed. A causal link to alcoholic beverage consumption and increased risks of certain types of cancer has been established although the risk for ethanol when used as an excipient in medicines would be considered negligible (see section 2.2.4) (Rehm et al., 2010 [96]).

People with or without epilepsy can have seizures after heavy drinking. They are most likely to happen between 6 and 48 hours after drinking and are known as alcohol withdrawal seizures. For people with epilepsy occasional or light and moderate alcohol-drinking is not associated with alcohol-related seizure occurrences and alcohol abstinence may not be necessary as long as epilepsy patients practice responsible alcohol intake (Hamerle et al., 2018 [35]).

Regular alcoholic beverage consumption can induce alcoholic liver disease. It has been estimated that 90% of persons who consume more than 60 g of alcohol per day, develop steatosis. However, significant fibrosis or cirrhosis only develops in up to 30% of this population (Hagström et al., 2017 [34]). Although drinking may have detrimental effects on health; low to moderate consumption of alcohol, below two drinks per day in women and three drinks per day in men, has not been associated with an increased risk for liver disease and the risks are considered acceptable in many countries (IARD [44]).

In most liver diseases alcohol consumption of more than 30 g per day in men and 20 g per day in women is associated with fibrosis progression, development of cirrhosis and hepatocellular carcinoma, and mortality (Hagström et al., 2017 [34]). With respect to low levels of alcohol consumption there is a lack of evidence in some conditions (e.g. autoimmune conditions, hemochromatosis). In other conditions there is uncertainty with conflicting evidence, e.g. chronic viral hepatitis C (HCV) (Hagström et al., 2017 [34]). In the most common liver disease, non-alcoholic fatty liver disease (NAFLD), there are possible benefits for some NAFLD-patients and increased risk for others (Ajmera et al., 2017 [1]).

The life-time risks of some cancers are increased by the consumption of alcoholic beverages; increased risks being found at as low as 1 drink per day (See section 2.2.4 for discussion). There remain unknowns at lower levels of exposure attributed to ethanol as a pharmaceutical excipient.

Cutaneous use

Products can contain enough ethanol to render them flammable. Alcoholic disinfectant solutions have been implicated in surgical fires causing burns to patients (Bonnel et al., 2015 [7]). Very occasionally accidental fires and burns to healthcare workers have been reported in association with alcohol based hand gels (O'Leary et al., 2011 [87]). Accidental ignition of ethanol containing sun screens and hairsprays have also been reported (FDA consumer updates 2013 [23]).

Topical ethanol generally has a low potential for irritancy although burning sensations can occur if the skin is pre-irritated (Löffler et al., 2008 [59]). Erythema with topically applied acetaldehyde has been noted and where enhanced penetration has been achieved (Lachenmeier, 2008 [52]). Ethanol does penetrate adult skin but studies have shown that systemic exposure only slightly above endogenous levels resulted even after excessive cutaneous exposure to ethanol, although, increased absorption across damaged skin has been noted (effects of ethanol on neonatal skin can be more significant - see under special populations). Ethanol is a penetration enhancer and may enhance the absorption of not only the active substance but other excipients (Lachenmeier, 2008 [52]).

4.2. Safety in special populations

Exposure to high levels of ethanol during pregnancy can result in foetal alcohol syndrome (FAS) or foetal alcohol spectrum disorder (FASD). Abnormalities include long-term brain dysfunction, behavioural problems, growth deficiencies, abnormal facial appearance and various other birth defects (Briggs et al., 2017 [10]). These effects are generally only observed with high levels of alcoholic beverage consumption during pregnancy. An unusual case of FAS has been reported when a woman consumed, throughout pregnancy, 480–840 ml/day of an over-the-counter cough preparation containing 7.6% w/v ethanol (equivalent to 36.5–65 g of ethanol/day). The infant had some of the typical features of the FAS (Chasnoff et al., 1981 [17]).

Exposure of ethanol from medicines is generally much lower than even a single alcoholic beverage. A study considering 32,870 women investigated the effects of consumption ranging from one alcoholic drink per day (12 g ethanol) to 6 or more drinks per day (36 g+ ethanol). Malformation rates were similar between non-drinkers and women drinking less than 2 drinks /day (24 g/day). Increased malformation rates were seen above this level and a significant trend was found with increasing alcohol use and congenital malformations (Mills et al., 1987 [75]).

There is some uncertainty on effect levels with some studies showing slight effects on birth weight in those drinking less than one drink/day (Wright et al., 1983 [107]).

A review considering exposure to light drinking (less than 32g ethanol per week) while pregnant, found limited evidence for a causal role of light drinking in pregnancy, compared with abstaining, on most of the outcomes examined. The chance of a small gestational age (SGA) and preterm birth were higher for babies whose mothers consumed up to 32 g/week versus none. However, there was a paucity of evidence, so effects might not have been detected (Mamluk et al., 2017 [63]).

Spontaneous abortion risk may also be increased by ethanol exposure. A two- to four- fold increase in the risk of spontaneous abortions and moderate drinking (>30 ml of absolute alcohol twice per week) has been found (Harlap et al., 1980 [36]; Kline et al., 1980 [50]).

With respect to "safe levels" during pregnancy there are many unknowns. Effects of ethanol seem less at low levels and exposure via medicines is expected to be much lower than in alcoholic beverage consumption, however, ethanol-abstinence in pregnancy is often recommended.

It is important to note that the effect of long term exposure to even low levels of ethanol in medicines on the health and development of children has not been evaluated (Fiocchi et al., 1999 [25]). The undeniable existence of FAS raises concern that there is at least, in theory, a risk to development from chronic exposure to ethanol during childhood.

Drinking alcoholic beverages can have an effect on breastfeeding. Oxytocin causes contraction of the smooth muscle affecting ejection of the milk. Women who had ingested ethanol (400 mg/kg) experienced a 78% decrease in AUC for oxytocin and an increase in latency time to milk ejection (Mennella et al., 2005 [72]). Children breastfed by women who had consumed alcohol (300 mg/kg) prior to feeding ingested 20% less milk in the first 4 hr after maternal alcohol consumption than otherwise (Mennella et al., 1993 [68]). But this was compensated for by a larger in take 8–12 hours after maternal alcohol consumption (Mennella, 2001 [70] ; Mennella et al., 1993 [68]). The initial reduction in milk consumptions have been attributed to the reduced milk yield after alcohol intake rather than any dislike for the taste of the milk (Mennella, 1997 [74]; Haastrup et al., 2014 [33]; Lawton, 1985 [55]).

Alcohol passes freely into breast milk, present in approximately the same amounts as maternal blood, being in dynamic equilibrium (Kesaniemi, 1974 [47]; Lawton, 1985 [55]). The metabolite acetaldehyde is not excreted into human milk, even at high concentrations in maternal blood (Kesaniemi, 1974 [47]).

A child when breast feeding would be exposed to only a small fraction of the ethanol consumed by the mother. It has been calculated that a child is exposed to approximately 5% of the weight-adjusted maternal dose assuming the child is breastfed at the time of maximum alcohol concentration in the milk. For example, if the mother's BAC was 100 mg/100 ml at the time of breastfeeding the child's peak BAC would be 5 mg/100 ml (Haastrup et al., 2014 [33]; Lawton, 1985 [55]).

Changes in the sleep patterns of children breastfed milk containing alcohol have been reported. Studies have shown that sleep was divided into shorter intervals but overall amounts of sleep were unchanged (Mennella et al., 1991 [69]; Mennella & Garcia-Gomez, 2001 [70]). A decrease in overall sleep of 25% has been reported (Mennella & Gerrish, 1998 [71]). The amount of active (REM) sleep was initially reduced for the first 3.5 hr and then increased for the next 20.5 hr (Mennella & Garcia-Gomez, 2001 [70]).

Traditions of drinking alcoholic beverages or foods enriched with ethanol whilst breast feeding exist. In Mexico 1-2 L of pulque (a drink with 3% alcohol) is sometimes consumed on a daily basis whilst pregnant or breast feeding. No difference in rate of growth in children at 6 months of age was noted when 32 children of women with daily pulque intake was compared to 62 without daily intake (Flores-Huerta et al., 1992 [26]). Another study showed statistically significantly poorer growth at 5 years of age, children of the women with the highest daily pulque intake during lactation (Backstrand et al., 2004 [5]).

A Chinese tradition involves the eating a chicken soup enriched with rice wine during the month postpartum. In a study maternal mean maximal BACs of about 30 mg/100 ml were achieved (Chien et al., 2005 [18]). Concerns regarding decreased lactation performance have been raised regarding this practice (Chien et al., 2008 [19]).

Some effects on infants' breast fed during this period have been reported. A 19-day old presented with abdominal distention and poor feeding for 4 days. Traces of BAC were present 23 hours after admission. The mother had reported taking the Chinese chicken /wine soup consecutively for 10 days. The suspected cause of abdominal distention was ethanol-induced ileus. Ethanol-induced acute reactive gastritis was also reported in a 3 week old whose mother consumed chick wine soup daily (Hon KL et al., 2016 [40]).

In some studies high-levels of alcohol use during the period of breastfeeding has been found to significantly compromise a child's development. A study of found that the children of the women with high alcohol intake found had statistically significantly lower scores on a scale of psychomotor development than the other children however, there was no difference with regard to mental development at 1 year according to the methods used (Little et al., 1989 [56]). In a subsequent study the same investigator could not reproduce the motor evaluation findings 18 months of age although there were less women with very high or alcohol consumption in this study (Little et al., 2002 [57]). Epidemiologic evidence from South Africa has been provided that by the age of 7 children of mother's who drank post-partum, engaging in regular and frequent binge drinking, had developmental traits associated with foetal alcohol spectrum disorders FASD. The authors state that children in were alcohol-exposed and unexposed in various combinations in both the prenatal and postpartum periods, but they were able to detect a general overall impact of alcohol delivered to the child through breastmilk via FASD diagnosis while controlling for proven confounders. However, it is also stated that due to the low socioeconomic status, and possible nutritional deficiencies in these communities the results may not apply to better nourished, more advantaged populations (May et al., 2016 [67]).

Considerable uncertainty exists as to the effects of exposure to ethanol in breast milk on the development of children. Uncertainty with regard to the long-term effects of ethanol consumption extends to older children. Effects on development have been detected in adolescents consuming high levels of alcohol. It has been found that alcohol-dependent adolescents demonstrated deficits in their retrieval of verbal and non-verbal information and in visuospatial functioning compared with adolescents with no history of alcohol dependence (Brown et al., 2000 [12]). A study in neonates being regularly dosed with oral liquid preparations containing ethanol (iron and furosemide) suggested that acetaldehyde blood levels were elevated compared to the control group (Pandya et al., 2016 [88]). These elevated levels were obtained with quite low doses of ethanol (median (range) 7.24 (2.27–78.42) mg ethanol/dose). The clinical significance of elevated acetaldehyde levels is unclear.

Lethal doses of ethanol are said to occur at lower doses in children (3 g/kg) compared to adults (5–8 g/kg) (Litovitz, 1986 [58]). Children are more sensitive than adults to some of the effects of ethanol. Relatively small amounts of ethanol can produce hypoglycaemia, especially in infants and young children with low glycogen stores. Signs of coma, hypoglycaemia and hypothermia may occur when the BAC exceeds 50–100 mg/100 ml. In older children and adolescents hypoglycemia is less common and intoxication causes effects similar to adults (Lamminpää et al., 1994 [53]).

Cutaneous use

In neonates, cutaneous absorption of ethanol is significant (especially under occlusion) due to the newborn's immature skin and this may lead to significant local reactions (e.g. haemorrhagic skin necrosis) and systemic toxicity (Mancini, 2004 [64]).

A case of skin necrosis in a pre-term neonate has been reported when ethanolic disinfectant initially applied for a procedure has dripped down to soak the surface on which the baby was lying. The underlying surface then acted as an occlusive dressing preventing evaporation ethanol and other alcohols. Haemorrhagic lesions on the back and buttocks were noted caused by local toxicity. The new born premature baby (27-week gestation) was cleansed with industrial methylated spirits (95% ethanol and 5% wood naphtha, which is at least 60% methanol) at age 1 hour prior to umbilical catheterisation. At 12 hours of age haemorrhagic lesions on the back and buttocks were noted. The distribution of damage to the skin suggested that the baby was lying in contact with the ethanolic skin disinfectant. Systemic absorption was also significant with blood ethanol concentrations 259 mg/100 ml and blood methanol 26 mg/ml. The child died at 48 hours; cardiac complications implicated (Harpin et al., 1982 [37]). Two cases of skin lesions have been reported with isopropyl

alcohol; one in similar circumstances and one when occluded under an ECG electrode (Schick et al., 1981 [97]). Similar demagogical effects have been noted with chlorhexidine solutions both alcohol based and aqueous, and recommendations to use with care in neonates, especially those born before 32 weeks of gestation and within the first 2 weeks of life have been made by the EMA (PRAC) (EMA/PRAC/490498/2014 [21]).

Percutaneous absorption of ethanol is increased when the barrier function of the skin is compromised. A child who had suffered scalding to hand and arm at 1 year of age was prepared for plastic surgery at 2 years of age with wrappings soaked with 70% ethanol. About 10% of the body surface area was covered on the evening prior to surgery. In the morning the child was comatose, tachycardic, hypoglycaemic and BAC was significantly raised (80 mg/100 ml). On removing the wrapping the skin was found to be haemorrhagic, blistered and partly detached (Püschel, 1981 [92]).

Percutaneous absorption of ethanol causing intoxication and fatal outcomes has been reported in older children. The practice of sponging with alcohol has been implicated. A 4-month old died after alcohol sponges had been applied (Niggemeyer & Zoepffel, 1964 [85]). A six-month-old became comatose and developed hypoglycaemia after 70% ethanol was applied by sponging for 13 hours prior to admission. BAC on admission was 220 mg/100 ml and blood glucose 22 mg/100 ml. Intravenous glucose was given and the child recovered uneventfully (Moss, 1970 [80]). Systemic toxicity in 28 children between 1 month and 33 months of age has been reported in Argentina in the 1960's, following application of alcohol-soaked cloths to relieve abdominal pain. Fatal outcomes were reported in two of these cases (Giménez et al., 1968 [29]).

The risk of systemic toxicity by percutaneous absorption of seems to decrease with age. The effects of percutaneous absorption under occlusion were studied in four children (7–9 years of age) and one adult. The legs from the feet to above the knees were wrapped in ethanol-soaked cotton (200 ml of 95% (v/v) ethanol) and occluded with rubber sheeting and adhesive tapes for 4–9 hours. No ethanol was measurable in the blood (Bowers et al., 1942 [8]).

5. Safety information relevant for the package leaflet

Systemic exposure to ethanol can affect reaction times and co-ordination. These effects are usually short term and the warnings in the package leaflet are based on each dose, rather than daily exposure. Patients may be taking part in activities such as riding bicycles or driving cars, so it is important that some warning of amounts of ethanol contained in medicines and the likely effects are given.

In all cases the amount of ethanol contained in a dose or volume of a medicine is given. As patients and carers may understand the percentage concentration of alcoholic beverages the ethanol content as a percentage is given. The equivalent amount of wine or beer in each dose or volume of medicine is also stated to further aid comprehension.

The three levels of warning are as follows.

- Below 15 mg/kg/dose the patient should experience no noticeable effects.
- In the middle range (15 mg to less than 75 mg/kg/dose) adults and older children should not experience any effect but effects on younger children are less certain.
- At the third level (75 mg/kg/dose and above) warnings are given that task performance may be affected in all age groups. This level is based on when effects first became apparent in studies in adults performing complex tasks.

Although consumption of alcoholic beverages can influence some disease conditions the low-levels of exposure via medicines is likely to be associated with less risk. Patients with liver diseases and should consult their healthcare professionals. Further uncertainties exist regarding pregnancy and breast-feeding and on a precautionary basis healthcare professional should be consulted.

Ethanol is used in preparations for the skin and warnings are given regarding pain on application to damaged skin. Where there is a risk of combustion a warning regarding the flammability of the product may be necessary. The skin of neonates is much more permeable to ethanol than adult skin. Significant local reactions and systemic toxicity have been noted in neonates exposed to cutaneous ethanol.

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Appendix 1 - Calculation of BAC: limitations and assumptions

The formula presented below makes many assumptions but may be used in the approximate estimation of blood alcohol concentration (BAC) rise. The assumptions generally over estimate BAC as a safety precaution (for example the equations assume complete and instantaneous absorption of orally ingested ethanol).

$$BAC\ (g/l) = \frac{\text{Ethanol (g)}}{Vd(l/kg) * BW(kg)}$$

BAC: blood alcohol concentration. If BAC is expressed in g/l, this value needs to be multiplied by 100 to be converted in mg/100ml or mg/dl (1 g/l = 100 mg/dl)

Ethanol: Ingested Ethanol (g) may be calculated from the concentration of ethanol and the volume of a single dose. The specific gravity of ethanol is 0.789 i.e. 1 ml weighs 0.789 g (0.8 may be used as an approximation). In calculating ingested ethanol it may be necessary to first convert the percentage v/v into percentage w/v. For example an ethanol (alcohol) concentration of 12.5%v/v corresponds to 10%w/v (12.5ml /100ml x 0.8= 10g/100ml). A 5-ml spoon of such a medicine would contain 0.5 g ethanol.

Vd: **Volume of distribution (l/kg)** is assumed to be 0.6 l/kg. This is a simplification which overestimates the BAC as a precautionary measure, in particular for children.

The volume of distribution (Vd) of ethanol is dependent on the water compartment of the body. Equations for estimating blood ethanol rises are based on the Widmark equation. It was recognised from experimental work that the Vd varied between individuals and Widmark assigned a Vd of 0.68 l/kg for males and as 0.55 l/kg for females (Widmark, 1981 [105]). The difference is thought to be related to the water compartment of the body and may partially explain differences in the ethanol toleration by the genders (Norberg et al., 2003 [86]). Neonates and children may have a larger water compartment than adolescents and adults. Water content has been reported to decrease from 92% in premature new-borns to 75% in full-term new-borns and then to 60% by age 1 (Lamminpää et al., 1995 [53]).

BW: Body weight (kg). Usually BW= 70 kg for an adult

Examples of calculation:

Example 1 (adult): Vd=0.6 l/kg; BW=70 kg; Ethanol intake=21 g (≈ one glass of wine):

BAC $= \frac{21}{0.6*70} = \mathbf{0.5\ g/l\ =\ 50\ mg/dl}$

Example 2 (child): Vd=0.6 l/kg; BW= 20kg; Ethanol intake =15 mg/kg (or 300 mg or 0.3g):

BAC= $\frac{15*20}{0.6*20} = \frac{15}{0.6} = 25\ mg/l\ =\ \mathbf{2.5\ mg/dl}$

or

BAC = $\frac{0.3}{0.6*20} =\ 0.025 g/l =\ 25 mg/l =\ \mathbf{2.5 mg/dl}$

Further tabulated example calculations:

Ethanol exposure (mg/kg/dose)	Predicted rise in BAC (mg/100ml)	Equivalent to exposure in 70kg adult (ethanol (g))	Equivalent amount of wine for a 70kg adult	Equivalent amount of beer for a 70kg adult	Threshold for information in the package leaflet
1	0.17 mg/100 ml	0.07 g	0.7 ml	1.8 ml	Zero to less than 15 mg/kg/dose
5	0.8 mg/100 ml	0.35 g	3.5 ml	9 ml	
15	2.5 mg/100 ml	1.05 g	10 ml	25 ml	15 mg/kg/dose to less than 75 mg/kg/dose
25	4.2 mg/100 ml	1.75 g	18 ml	44 ml	
50	8.3 mg/100 ml	3.5 g	35 ml	88 ml	
75	12.5 mg/100 ml	5.25 g	50 ml	125 ml	75 mg/kg/dose and more
100	16.7 mg/100 ml	7.0 g	70 ml	175 ml	
150	25 mg/100 ml	10.5 g	105 ml	260 ml	
300	50 mg/100 ml	21.0 g	210 ml	525 ml	
600	100 mg/100 ml	42.0 g	420 ml	1050 ml	

Appendix 2 - Information in the package leaflet as per 2003 Guideline [3]

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Ethanol	Oral and Parenteral	Less than 100 mg per dose	This medicinal product contains small amounts of ethanol (alcohol), less than 100mg per <dose>.	This statement is to provide reassurance to parents and children concerning the low levels of alcohol in the product.
		100 mg – 3 g per dose	This medicinal product contains ... vol % ethanol (alcohol), i.e. up to ... mg per dose, equivalent to ... mL beer, ... mL wine per dose. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease, or epilepsy.	The package leaflet should give the equivalent volume of beer and wine, nominally calculated assuming 5 % vol and 12% vol ethanol respectively. Separate warning statements may be needed in different parts of the PL.
		3 g per dose	This medicinal product contains ... vol % ethanol (alcohol), i.e. up to ... mg per dose, equivalent to ... mL beer, ... mL wine per dose. Harmful for those suffering from alcoholism. To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease or epilepsy. The amount of alcohol in this medicinal product may alter the effects of other medicines. The amount of alcohol in this medicinal product may impair your ability to drive or use machines.	