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# Questions and answers on cyclodextrins in the context of the revision of the guideline on 'Excipients in the label and package leaflet of medicinal products for human use' (CPMP/463/00 Rev. 1)

Draft

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# Questions and answers on cyclodextrins in the context of the revision of the guideline on 'Excipients in the label and package leaflet of medicinal products for human use' (CPMP/463/00 Rev. 1)

## 1. Background

Following the European Commission decision to revise the Annex of the guideline on 'Excipients in the label and package leaflet of medicinal products for human use' (CPMP/463/00 Rev. 1) [1], a multidisciplinary group of experts involving SWP (lead), QWP, PDCO, PRAC (ex PVWP), CMD(h), VWP, BWP and BPWP was created in 2011.

The objective of this group is to update the labelling of selected excipients listed in the Annex of the above mentioned EC guideline, as well as to add new excipients to the list, based on a review of their safety. The main safety aspects to be addressed were summarised in a concept paper published in March 2012 [2].

Draft Q&A documents on excipients are progressively released for public consultation. They include proposals for new or updated information for the labelling and package leaflet. The corresponding background report supporting the review is published for information only.

When one or several Q&As have been finalised, the Annex of the guideline is revised, including the new information and a timeframe for implementation.

## 2. What are cyclodextrins and why are they used as excipients?

Cyclodextrins (CDs) are cyclic oligosaccharides made up of a number of dextrose units of (α-1,4)-linked α-D-glucopyranose. These cyclic structures contain a lipophilic central cavity and a hydrophilic outer surface (**Fig. 1**). Cyclodextrins are made up of six, seven or eight dextrose units (α-, β-, and γ-CDs, respectively; the so-called parent cyclodextrins). Cyclodextrins interact with hydrophobic drug molecules to form inclusion complexes and can be used e.g. to improve the aqueous solubility of the drug molecule. For β-CD, which itself has a relatively low aqueous solubility, substitution of any of the hydrogen bond-forming hydroxyl groups, even by lipophilic functions, results in a dramatic improvement in the aqueous solubility of the derivative. Examples of β-CD derivatives used as excipients in medicines are the sulfobutylether of β-CD (SBE-β-CD), the hydroxypropyl derivative of β-CD (HP-β-CD), and the randomly methylated β-CD (RM-β-CD).

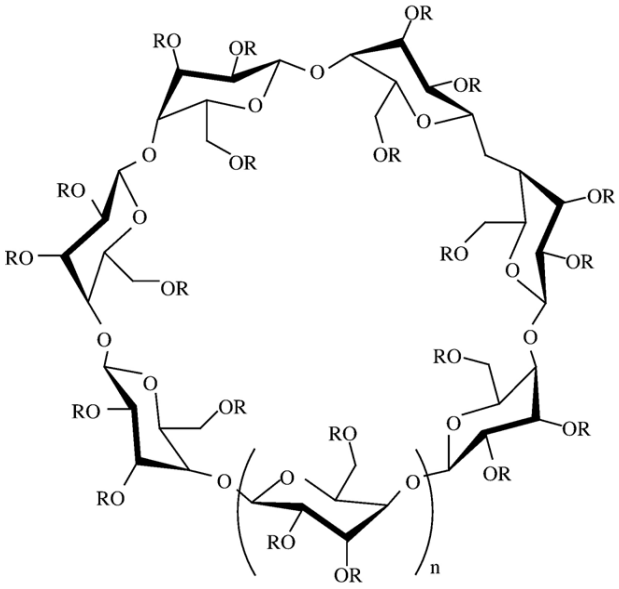



**Figure 1: β–Cyclodextrin structure**

SBE-β-CD: R = $-(CH_2)_4–SO_3^-Na^+$

HP-β-CD: R = $-CH_2–CHOH-CH_3$

RM-β-CD: R = $-CH_3$

In the pharmaceutical industry, cyclodextrins have mainly been used as complexing agents to increase the aqueous solubility of active substances poorly soluble in water, in order to increase their bioavailability and to improve stability. In addition, cyclodextrins can be used to reduce or prevent gastrointestinal and ocular irritation, reduce or eliminate unpleasant smells or tastes, prevent drug-drug or drug-additive interactions within a formulation (all these properties are based on reduction of the free drug in solution), or to convert oils and liquid drugs into microcrystalline or amorphous powders [3].

# 3. Which medicinal products contain cyclodextrins?

Because of the diverse types of application of cyclodextrins, several types of medicinal products can contain cyclodextrins. They are used e.g. in tablets, aqueous parenteral solutions, nasal sprays and eye drop solutions. Examples of the use of cyclodextrins in medicines on the European market are β-CD in cetirizine tablets and cisapride suppositories, γ-CD in minoxidil solution, and examples of the use of β-cyclodextrin derivatives are SBE-β-CD in the intravenous antimycotic voriconazole, HP-β-CD in the antifungal itraconazole, intravenous and oral solutions, and RM-β-CD in a nasal spray for hormone replacement therapy by 17β-estradiol. In Germany and Japan there are infusion products on the market, containing alprostadil (prostaglandin E1, PGE1) with α-CD [4].

Cyclodextrins used as an active substance, rather than excipients, will not be discussed in this document (not in the scope).

# 4. What are the safety concerns?

## 4.1 Oral products

The oral availability of cyclodextrins is very low. Adverse interactions with vitamins or other nutrients are not to be expected [5,6]. At high doses (> 1000 mg/kg/day) cyclodextrins may cause reversible

diarrhea and cecal enlargement in animals, and therefore also in humans to some minimum extent [7]. There are no data on children under two years old.

### 4.2 Nasal and pulmonary products

Cyclodextrins are absorbed poorly via mucosal membranes, but at high doses they can increase nasal and pulmonary drug permeability by direct action on mucosal membranes and facilitate also their own absorption. They can also strongly potentiate lipophilic absorption enhancers.

Less than 10% HP-β-CD or RM-β-CD solutions, and less than 1.5% β-CD solutions do not induce tissue damage in rats and can keep the integrity of the nasal mucosa [8].

### 4.3 Rectal products

Cyclodextrins can act as rectal absorption enhancers of drugs, including themselves; at higher amounts of cyclodextrins, a higher percentage of cyclodextrins is absorbed. In rats, up to 5% of β-CD and 26% of HP-β-CD can be absorbed. Suppositories with up to 230 mg of β-CD and 12% of HP-β-CD do not cause irritation in rectal mucosa in humans and rabbits respectively. However, α-CD potentially causes damage to the epithelial cell layer [8].

### 4.4 Dermal products

Cyclodextrins alone are poorly absorbed transdermally, but in combination with absorption-promoting agents, they are able to permeate the skin by 12%, 43%, and 53% for β-CD, RM-β-CD, and HP-β-CD, respectively. Concentrations up to 0.1% of α-, β-, and γ-cyclodextrins are considered safe.

Studies on antigenicity, mutagenicity, and topical irritation have proven that HP-β-CD is as safe as materials currently being used in perfumes and cosmetics [9].

### 4.5 Ocular products

Cyclodextrins enhance drug penetration into the eye. Concentrations of 4% α-CD and 5% RM-β-CD can be toxic to the corneal epithelium of rabbits. Solutions of 10% SBE-β-CD and 12.5% HP-β-CD are found not to be toxic or irritating in rabbit eyes [7].

### 4.6 Parenteral products

IV-administered CDs disappear rapidly from systemic circulation and are renally excreted intact. The t½ varies from 20 to 100 minutes, with the exception of RM-β-CD, which has a t½ of 7h [7].

Alpha-CD, β-CD and RM-β-CD showed renal toxicity at relatively low doses after parenteral administration and thus seem not very suitable for medicinal products given intravenously. High doses of $\geqslant$600 mg/kg of $\gamma$-CD showed only reversible vacuolation in the renal tubular epithelium of rats [10].

HP-β-CD and SBE-β-CD at high doses can cause vacuolation of the kidney tubular cells without loss of kidney function in animals. This transient increase in size of apical vacuoles is also observed as an adaptive response to the excretion of osmotic agents such as glucose, mannitol and dextran at extremely high concentrations. Longer treatments cause these mostly reversible effects, at lower doses of SBE-β-CD and HP-β-CD, indicating that duration of exposure may be of importance. HP-β-CD and SBE-β-CD are considered safe at relatively high doses and used most widely in parenteral products. Amounts of ca 250 mg/kg/day are found safe in humans older than 2 years when given 21 days (HP-β-CD) or 6 months (SBE-β-CD). Because of their lower renal function, children less than 2 years old may theoretically be less vulnerable to renal toxicity. However, a few cases on the use of intravenous products with high doses of HP-β-CD and SBE-β-CD in neonates and young children have been reported without signs of toxicity [11,12,7].

## 5. What are the reasons for giving information in the package leaflet?

Cyclodextrins are currently not included in the European Commission Guideline on excipients in the label and package leaflet of medicinal products for human use [1].

Although the oral availability of cyclodextrins is very low, high doses may cause reversible diarrhea and cecal enlargement in animals, and therefore also in humans to some minimum extent.

Depending on their amount, cyclodextrins may influence the permeability of tissues and therefore the bioavailability of active substances given topically (nasal, rectal, dermal, ocular).

Cyclodextrins can cause nephrotoxic effects in animals at high systemic exposure. Up to now, there is no proof of these effects in humans; however, data in children less than 2 years old are scarce.

In conclusion, safety information in the package leaflet may be desirable in products with substantial contents of cyclodextrins as excipient. However, because of limited information and possible interaction with active substances, the presence of cyclodextrins should be stated as a precaution (zero thresholds).

### *Current information in the package leaflet*

None.

128 # 6. Proposal for information in the package leaflet

| Name | Route of Administration | Threshold* mg/kg/day or % | Information for the Package Leaflet | Comments (for health care professionals) |
|---|---|---|---|---|
| **Cyclodextrins**<br>**eg.**<br>**α-cyclodextrin**<br>**β-cyclodextrin**<br>**γ-cyclodextrin**<br>**Sulfobutyl-ether-β-cyclodextrin (SBE-β-CD)**<br>**Hydroxy-propyl-β-cyclodextrin (HP-ß-CD)**<br>**Randomly methylated β-cyclodextrin (RM-β-CD)** | All routes of administration | zero | The amount of cyclodextrin in each <volume/unit> is xx mg.<br>Talk to your doctor or pharmacist before giving this medicine to your child if (s)he is less than 2 years as the cyclodextrin contained in this medicine might cause undesirable effects.<br>The presence of cyclodextrin in this medicine may alter the effects of other medicines. | Low doses of cyclodextrins are not expected to cause adverse effects. However, there is insufficient information on children less than 2 years.<br>The interactions of cyclodextrin should be stated and documented in the SmPC section 4.5). |
| | Oral | zero | *As above and:*<br>May cause intestinal disorders like diarrhoea. | At high dose (> 1000 mg/kg/day) cyclodextrins can cause reversible diarrhoea and cecal enlargement in animals. |
| | Parenteral | zero | *As above (in "all routes of administration") and:*<br>Before taking this medicine, talk to your doctor if you have a kidney disease. | At high dose (> 50-300 mg/kg/day) cyclodextrins can cause renal toxicity in animals when given intravenously.<br>In children less than 2 years, the lower glomerular function may protect against renal toxicity, but can lead to higher blood levels of cyclodextrins which may lead to extra-renal adverse effects. |

| Name | Route of Administration | Threshold* mg/kg/day or % | Information for the Package Leaflet | Comments (for health care professionals) |
|---|---|---|---|---|
| | | | | In patients with moderate to severe renal dysfunction accumulation of cyclodextrins occurs.<br><br>So far, there are no cases of kidney injury caused by cyclodextrins in humans. |
| | Ocular, dermal, rectal, nasal | zero | *As above (in "all routes of administration") and:*<br><br>May cause irritation. | At high concentration (>> 1%) cyclodextrins can be toxic to the corneal epithelium of rabbits.<br><br>At high concentration (>> 0.1%) cyclodextrins may cause damage to the skin.<br><br>At high doses (>> 5 mg/kg) cyclodextrins may cause damage to the rectal mucous epithelium.<br><br>At high concentration (> 10%) cyclodextrins can cause damage to the nasal mucosa of rats. |

Note:

* The threshold is a value, equal to or above which it is necessary to provide the information stated for the package leaflet. This threshold is not a highest acceptable limit. A threshold of 'zero' means that it is necessary to state the information in all cases where the excipient is present in the medicinal product [1].

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