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Information for the package leaflet regarding dextrans used as excipients 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 labelling and package leaflet of medicinal products for human use' [1, 3].

Dextran is a bacterial polysaccharide produced at the industrial level by the fermentation of sucrose-rich media. Dextrans have found industrial applications in food, pharmaceutical and chemical industries as adjuvant, emulsifier, carrier and stabiliser.

Dextrans as an active substance, including 40, 60, 70, and 75 dextrans, have been widely used for postoperative thromboembolic prophylaxis and as plasma volume expanders. Recently, dextrans have shown the potential to be used in several medicines and gene delivery systems to improve the stability but they also have been extensively utilised as controlled release polymer excipients in the preparation of oral hydrophilic matrix tablets.

The main adverse effects of dextrans are hypersensitivity reactions to intravenous dextran therapy and to dextran used in vaccines, as well as increase blood sugar level.

Dextrans have been included in the Annex of the guideline on 'Excipients in the label and package leaflet of medicinal products for human use' [1] because they are recently widely used as excipients in many formulation of medicines and can lead to serious adverse effects in patients hypersensitive to these.

50 # Proposal for new information in the package leaflet

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Dextrans	Parenteral and inhalation	Zero	This medicine contains x mg of dextran(s)* in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>. Rarely, dextrans can cause severe allergic reactions. If you have breathing difficulty or swelling or you feel faint, get medical help at once.	Dextrans can cause anaphylactoid reactions in some patients. ** The type of dextran(s) (e.g. dextran 70, dextran 40) in the medicinal product should be mentioned here.*

Scientific background

1. Characteristics

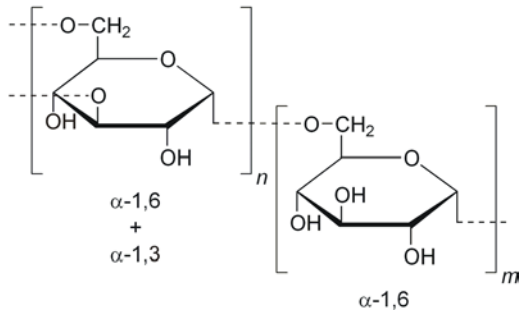
1.1. Category (function)

Dextrans are complex polysaccharides made of many glucose molecules composed of chains of varying lengths (from 3 to 2000 kilodaltons). The straight chain consists of α-1,6 glycosidic linkages between glucose molecules, while branches begin from α-1,3 linkages.

- **Class 1 dextrans** contain the α (1→6)-linked D-glucopyranosyl backbone modified with small side chains of D-glucose branches with α(1→2), α(1→3), and α (1→4)-linkage. The class 1 dextrans vary in their molecular weight, spatial arrangement, type and degree of branching, and length of branch chains, depending on the microbial producing strains and cultivation conditions.
- **Class 2 dextrans** (alternans) contain a backbone structure of alternating α (1→3) and α (1→6)-linked D-glucopyranosyl units with α (1→3)-linked branches.
- **Class 3 dextrans** (mutans) have a backbone structure of consecutive α (1→3)-linked D-glucopyranosyl units with α (1→6)-linked branches.

1.2. Physico-chemical Properties

The physical and chemical properties of purified dextrans vary depending on the microbial strains from which they are produced and on the production method. Dextrans have high water solubility and the solutions behave as Newtonian fluids. Solution viscosity depends on concentration, temperature, and molecular weight, which have a characteristic distribution. The hydroxyl groups present in dextran offer many sites for derivatisation, and the functionalised glycoconjugates represent a largely unexplored class of biocompatible and environmentally safe compounds.



CAS:	90004-54-0
Molecular formula:	$H(C_6H_{10}O_5)_xOH$
Mr:	variable

1.3. Use in medicinal products

There are four “Dex-ingredients” derived from starch (dextrans, dextrose, dextrates, dextrins) used for pharmaceutical purposes:

Dextrans	sugar molecules

Dextrates mix of sugars resulting from the controlled enzymatic hydrolysis of starch

Dextrins result from the hydrolysis of starch (primarily corn or potato) by heat or hydrochloric acid. It can also be obtained from wheat, rice or tapioca

Dextrose a sugar that is obtained from corn starch

Dextrans come from corn and potato starch; dextrose comes from corn. They are not a concern for coeliac disease patients.

Dextrates and Dextrins can come from any starch source including wheat starch which can contain low level of gluten (controlled by the manufacture). Therefore residual levels of gluten in dextrins are expected to be very low and are not a concern for coeliac disease patients either.

Dextrans are used as an osmotic agent in vaccines such as BCG or measles-mumps-rubella (MMR) vaccines. They are used as an antithrombotic (anti-platelet) agent – to decrease vascular thrombosis. Dextrans also reduce factor VIII-Ag Von Willebrand factor, thereby decreasing platelet function. Larger dextrans, which do not pass out of the vessels, are potent osmotic agents (volume expanders in anaemia), and thus are used in emergency services to treat hypovolemia. The larger dextrans (> 60000 Da) are poorly excreted from the kidney and prolonged antithrombotic and colloidal effects. Dextrans are also used in some eye drops as a lubricant and in certain intravenous fluids to solubilise other factors, e.g. iron (= iron dextran).

2. Pharmaco-toxicological data

2.1. Pharmacodynamic (if applicable)

2.2. Toxicology

Dextran sodium sulphate (DSS) toxicity after single administration

Product	**Species**	**Route**	**LD_{50}**
DSS (7500 Da)	Mouse	I.V	2.12 g/kg
DSS (25 kDa)	Mouse	I.V	2.35 g/kg
DSS (25 kDa)	Mouse	oral	0.473 g/kg
DSS (25 kDa)	Rat	I.V	2.35 g/kg
DSS (25 kDa)	Rat	oral	20.6 g/kg
DSS (25 kDa)	Rabbit	I.V	19 g/kg
DSS (47 kDa)	Mouse	I.V	0.573 g/kg
DSS (458 kDa)	Mouse	I.V	0.154 g/kg

Dextran sodium sulphate (DSS) toxicity after repeated administration

Species	Route	Duration	Dose	Observations	Reference
Rat	oral	30 days	2 g/kg/day	• Endocrine - other changes • Blood: changes in spleen • Enzyme inhibition, induction, or change in blood or tissue levels - phosphatases	Kiso, 1979 [12]
Rat	oral	24 W	1.59 g/kg/day	• Endocrine changes in thymus weight • Blood: normocytic anemia • Death	Oyo Yakuri, 1972 [21]
Rat	oral	4 W	3.2 g/kg/day	• Effects on liver, kidney, ureter, bladder • Death	Oyo Yakuri, 1972 [21]
Rabbit	I.V	15 W	10–50 mg/kg/day 5 days /week	• Increasing weakness • Paresis of the hind legs • Spontaneous fractures	Hint, 1958 [7]

DSS have been widely used for inducing colitis as inflammatory bowel diseases (IBD) model in various animal species. It has been shown that differential susceptibility to DSS-induced colitis happen between species and even inside strains of the same specie (Mähler, 1998 [16]; Stevceva, 1999 [29]). In rats, concentration of DSS required for inducing experimental colitis, are higher than in mice (5 % DSS solutions in drinking water vs 1–5%).

Mechanisms of colitis and effects have been studied in mice and rats (Trivedi, 2012 [32]; Tardieu, 1998 [31]). Westbrook et al. (2009 [33, 34]) have reported that intestinal mucosal inflammation, in ulcerative colitis-induced mice, would lead to systemic genotoxicity due to oxidative stress. Ulcerative colitis leads to a rise of inflammatory markers (e.g. IL-6, TNF-α, NFκB, and COX-2).

Mice treated (cycles of 7 days followed by 14 days of normal drinking water, 1 to 3 cycles) with 3% (w/v) DSS (Mw 36-40 kDa) dissolved in drinking water. Animal treated, have highlighted significant decreases in the body weight, colon length, GSH levels, and increases in malondialdehyde (MDA), myeloperoxidase (MPO) level, NFκB, and COX-2 expression in the colon and IL-6, TNF-α and PG-E2 levels in the plasma, compare to control group. Oxidative stress-induced DNA damage in colon was confirmed with modified comet assay using lesion specific enzymes (endonuclease III and FPG) and immunostaining of 8-oxo-DG. In addition, a significant increase in the micronuclei frequency in the peripheral blood has been reported.

122 *Dextran (CAS number: 9004-54-0) toxicity after single administration*

Species	Route	LD_{50}	Reference
Mouse	I.V	12 g/kg	Oyo Yakuri, 1972 [21]
Mouse	Oral	> 12.1 g/kg	Oyo Yakuri, 1972 [21]
Mouse	subcutaneous	> 12.1 g/kg	Oyo Yakuri, 1972 [21]
Rat	IV	6.9 g/kg	Oyo Yakuri, 1972 [21]
Rat	oral	> 3 g/kg	Oyo Yakuri, 1972 [21]
Rat	subcutaneous	10.7 g/kg	Oyo Yakuri, 1972 [21]
Rabbit	I.V	208 g/kg	Yakuri to Chiryo, 1975 [35]
Rabbit	I.V	17.4 g/kg	Oyo Yakuri, 1972 [21]

123 *Dextran 40 toxicity after repeated administration*

Species	Route	Duration	Dose	Observations	Reference
Rabbit	I.V	30 days	900 ml/kg/30 d-C	• Liver: Changes in liver weight • Endocrine: changes in adrenal weight • Blood: normocytic anemia	Oyo Yakuri, 1972 [23]
Rabbit	I.V	13 W-I	4680 ml/kg/13W-I	• Liver: Changes in liver weight • Blood: normocytic anemia • Death	Oyo Yakuri, 1972 [24]
Rabbit	I.V	26 W-I	3210 ml/kg/26W-I	• Liver: Changes in liver weight • Blood: normocytic anemia, changes in serum composition (TP, bilirubin, cholesterol…)	Yakuri to Chiryo, 1975 [35]

124 *Genotoxicity dextran (CAS number: 9004-54-0)*

125 Conventional genotoxic in vitro assays (such as Ames test and MLATK) have been performed and were
126 negative.

127 Ames test

Strain	Dose range (µg/plate)	Metabolic activation	Result	Reference
TA98	100-10000	none	negative	National cancer institute, 1995 [15]
TA98	100-10000	rat liver S9	negative	National cancer institute, 1995 [15]
TA100	100-10000	none	negative	National cancer institute, 1995 [15]
TA100	100-10000	rat liver S9	negative	National cancer institute, 1995 [15]
TA100	100-10000	hamster liver S9	negative	National cancer institute, 1995 [15]
TA1535	100-10000	none	negative	National cancer institute, 1995 [15]
TA1535	100-10000	rat liver S9	negative	National cancer institute, 1995 [15]
TA1535	100-10000	hamster liver S9	negative	National cancer institute, 1995 [15]
TA1537	100-10000	none	negative	National cancer institute, 1995 [15]
TA1537	100-10000	rat liver S9	negative	National cancer institute, 1995 [15]
TA1537	100-10000	hamster liver S9	negative	National cancer institute, 1995 [15]
TA1538	100-10000	none	negative	National cancer institute, 1995 [15]
TA1538	100-10000	rat liver S9	negative	National cancer institute, 1995 [15]
TA1538	100-10000	hamster liver S9	negative	National cancer institute, 1995 [15]

128 Mouse lymphoma TK assay

Cell	Dose range (µg/plate)	Metabolic activation	Result	Reference
L5178Y ($tk^+/^-$)	1000-5000	none	negative	Seifried et al.,2006 [27]
L5178Y ($tk^+/^-$)	1000-5000	Rat liver S9	negative	Seifried et al.,2006 [27]

Dextran was reported not to induce chromosomal aberrations in cultured Chinese hamster fibroblasts (Ishidate et al, 1978 [11]).

Carcinogenicity

DSS induces intestinal tumours in rats when given orally (Hirono et al [8, 9]).Carcinogenic potential of DSS given orally (2.5% diet) to 6-week-old inbred ACI rats, did appear to be in relation to its molecular weight as described by Hirono et al (1983 [10]). DSS (520 kDa) and DSS (9.5 kDa) diet induced colorectal squamous metaplasia but few intestinal tumours. Lack of squamous metaplasia and intestinal tumours in rats fed with dextran (21.5 kDa) may be attributable to the sulphur content. It has to be noticed that supplements of 0.25–0.5% for 82 weeks in rats did not increase the incidence of infection or tumours.

Product	Species	Route	Duration	Dose	Observations	Reference
DSS	rat	oral	94 W	0.5 g/kg/day	• Colon tumours	Hirono et al., 1982 [9]
DSS	rat	oral	69 W	1.4 kg/kg/day	• Colon tumours • Endocrine tumours	Hirono et al., 1982 [9]

Reproductive function toxicity

There is a lack of data regarding dextran's effects on the reproductive and development toxicity.

Product	Species	Route	Sex / Duration	Dose	Observations	Reference
Dextran 70	rabbit	I.V	female 8-16 day(s) after conception	675 g/kg/9 days LOAEL	• Effects on extra-embryonic structures (e.g., placenta, umbilical cord) • Foetotoxicity (except death, e.g., stunted foetus) • Developmental abnormalities: musculoskeletal system	Oyo Yakuri, 1972 [25]
Dextran 70	rabbit	I.V	male 91 day(s) pre-mating	3640 g/kg/91 days LOAEL	• Effects on prostate, seminal vesicle, Cowper's gland, accessory glands	Yakuri to Chiryo, 1975 [35]

Effects on immune response

Dextrans and DSS are able to activate an immune response from the host after administration.

It has been reported that DSS administrated (i.p 50 mg/kg) to mice led to an increase of the susceptibility of mice to bacterial infection (Hahn et al, 1974 [4]). This is in direct relation with the

toxic effects of sulphate on the mononuclear phagocytes since exposure of macrophages to DSS leads to an accumulation within the secondary lysosomes and an inhibition of the phagosome-lysosome interaction and might interfere with the enzymes in charge of killing bacteria.

Siebeck et al (1985 [28]) have reported that DSS (500 kDa) activates contact system and mediates arterial hypotension via B2 kinin receptors, in minipigs after I.V administration (bolus 5 mg/kg for 1 h). DSS infusion produces activation of the system of blood coagulation leading to high kinin levels in blood, a decrease in uncleaved kinogen in plasma; a severe transient arterial hypotension (via stimulation of the B2 kinin receptor) accompanied by vasodilatation and complement activation. These effects were highlighted by co-administration of Bay (a plasma kallikrein inhibitor) and/or Hoe-104 (a bradykinin B2-receptor antagonist) that were able to block DSS-induced hypotension.

Dextran induced anaphylactoid reactions (DIAR) in less than 1% of patients who received infusion of clinical dextran (Hedin, 1997 [5]). Incidence of reactions appeared to be related to chemical structure, the ones having higher molecular weights and/or a greater proportion of non–1.6-linkages causing a greater incidence of untoward reactions. Hypersensitivity reactions observed in the initial development of dextran as a blood extender are now reduced due to a modification of the dextran and by a pre-treatment of the patients with a low molecular weight dextran as monovalent hapten (Hedin, 1997 [5]). Regarding DIAR, it is questionable how animal models can be used to extrapolate data to human.

When dextrans are used as vector in drug delivery or as coating, physical interactions between dextran and ‘encapsulated’ can enhance allergic reactions, therefore a case by case study should be considered.

2.3. Toxicokinetics

As a blood extender dextran is not distributed in body tissues. Dextran is metabolised to monosaccharides mainly glucose.

3. Pharmacokinetics (in humans)

Molecular-weight influence of fluorescein-labeled dextrans on the PK parameters in adult SD rats, have been reported by Mehvar and Shepard (Mehvar, 1992 [17]). Effects of single I.V administration (5 mg/kg) of dextrans (4 kDa, 20 kDa, 40 kDa,70 kDa and 150 kDa) and single oral doses (50 mg/kg) of dextrans (4 kDa, 20 kDa, and 40 kDa) were studied. After oral administration, all the tested items were not detected in serum and negligible levels were absorbed on the systemic circulation (< 0.4% of the dose). Lack of bioavailability after oral administration is due to the size (radius) of dextrans preventing their passage through the epithelial junctions or aqueous pores of the gastrointestinal tract. Koyama et al (1996, [13]) have demonstrated that dextran of high molecular weight (M_W) are degraded into lower M_W derivatives during the permeation across the epithelial cells of GI tract. Presence of receptors with specificity for dextrans involved for the transport through the mucous membrane, have been shown. After I.V administration, concentrations of dextrans (40, 70 and 150 kDa) are detected in serum samples 12 h after the dosing whereas concentrations of dextran 4 kDa and 20 kDa cannot be detected in serum samples beyond 3 and 1.5 h respectively. Therefore, kinetic parameters exhibit Mw dependency. Nevertheless this dependency has to be connected with renal clearance and volume of distribution.

Regarding the metabolism, dextrans are depolymerised by dextranases (α-1-glucosidases) present in in various organs such as liver, spleen, kidney and the lower part of the gastrointestinal tract. Liver and spleen have a highest concentration of dextranases. In the liver, elimination of dextrans can occur

through excretion into the bile (Lake, 1985 [14]) in addition to metabolism by dextranases but depolymerisation process appears to be related with the Mw as expected.

Low Mw dextrans are excreted unchanged in urine whereas higher ones are substantially accumulated in the liver and the spleen. Distribution to over tissues such as brain, lung and heart appears negligible. Nevertheless, higher Mw dextrans can accumulate in the lymph nodes. Overall, a molecular weight and dose dependency for tissue accumulation has been shown (Mehvar et al., 1994 [18]; 1995 [19]).

Takakura et al (1990, [30]) have demonstrated that the overall electric could have a significant impact on the plasma and tissue disposition of dextrans. Negative charged dextrans have a prolonged residence in the systemic circulation and minor uptake by the tissues. This higher residence time compared with positively charged dextrans is related to negative charges on the biological membrane surfaces.

Overall, when dextrans are used as a vector in drug delivery, pharmacokinetic of the whole system has to be considered.

4. Clinical safety data

The dextrans can cause more severe anaphylactic reactions than the gelatines or the starches. The reactions are due to dextran reactive antibodies which trigger the release of vasoactive mediators. Incidence of reactions can be reduced by pre-treatment with a hapten (Dextran 1).

Side-effects can be very serious (anaphylaxis, volume overload, pulmonary oedema, cerebral oedema, or platelet dysfunction). This has been serious enough for some parenteral iron preparations to be withdrawn by the FDA, e.g. Imferon®, withdrawn in 1990.

Use of dextran medication to prevent hypotension risk during delivery should be considered with care. There are some reports in the literature of maternal anaphylactoid reaction with apparent death in a neonate after dextran administration to the mother (P. Babier, 1992 [2]).

Incidence of reactions appeared to be related to the chemical structure of the dextrans; the dextrans having higher molecular weights and/or a greater proportion of non–1.6-linkages cause a greater incidence of untoward reactions. Hypersensitivity reactions are observed in the initial development of dextran as a blood extender. The occurrence of anaphylactoid/anaphylactic reactions in some patients has been attributed to antibodies of the IgG class formed after ingestion or of immunologically cross reacting polysaccharides in foods (Hedin, 1981 [6]).

Orally ingested dextrans are rapidly converted to glucose. Therefore diabetics could be considered as a risk group for bakery products containing significant level of dextrans (SCCS 2000 [20]). This is not considered to be a relevant concern for the use of dextrans as excipients in medicinal products.

5. Safety information relevant for the package leaflet

The main adverse effects of dextrans are hypersensitivity reactions to intravenous dextran therapy which have been recognised since the 1960s. Also hypersensitivity reactions to dextran used in vaccines as an excipient osmotic agent have been reported by various authors. Dextran-induced anaphylactoid reaction (DIAR) is a rare but severe complication. Therefore a statement about the risk of severe allergic reactions is proposed to be included in the package leaflet. Appropriate treatment should be initiated rapidly when DIAR is suspected.

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