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Information for the package leaflet regarding dextrans used as excipients in medicinal products for human use

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Table of contents

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' [1,5].

Dextran is a bacterial polysaccharide produced at industrial level by the fermentation of sucrose-rich media. Dextrans are found in industrial applications in food, pharmaceutical and chemical industries where they are used 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. However, this document specifically concerns dextrans used in medicinal products as excipients. Recently, dextrans have shown the potential to be used in several medicines and gene delivery systems to improve stability. They have been studied as controlled-release polymer excipients in the preparation of oral hydrophilic matrix tablets. Additionally, their application as excipients in the development of nanometric vectors has been identified as an interesting avenue for expanding their use. This advancement plays an important role in the solubilisation and vectorisation of active substances, as well as offering new possibilities in drug delivery, therapeutic methodologies, and expanders.

Although dextrans are excipients generally safe to use, they may cause hypersensitivity and severe allergic reactions including anaphylactoid shocks, that can be lethal and therefore demand careful consideration. This is why it is proposed to include dextrans to the Annex of the guideline on 'Excipients in the label and package leaflet of medicinal products for human use' [1]. Dextrans have recently been widely used as excipients in many formulation of medicines but can lead to serious adverse effects in patients hypersensitive to these excipients when used in parenteral and inhalation formulations.

Proposal for new information in the package leaflet

Name	Route of Administration	Threshold	Information for the Package Leaflet	Comments
Dextrans e.g. dextran 1 for injection, dextran 40 for injection, dextran 60 for injection, dextran 70 for injection	Parenteral and inhalation	Zero	This medicine contains x mg of dextran(s) <type> in each <dosage unit><unit volume> <which is equivalent to x mg/<weight><volume>>. Dextrans may cause sudden, severe allergic reactions with symptoms including breathing difficulty, swelling, light-headedness, fast heartbeat, sweating and loss of consciousness. Seek medical attention immediately if you experience any of these symptoms.	

Scientific background

1. Characteristics

1.1. Category (function)

Dextrans are complex polysaccharides made of many glucose molecules composed of chains of varying lengths (from 1 kilodaltons to 2000 kilodaltons). They are mixtures of polysaccharides in which the glucosidic bonds are principally of the α-1-6 type.

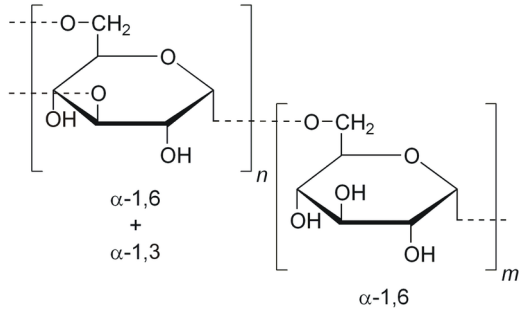
1.2. Physico-chemical Properties

The physical and chemical properties of purified dextrans vary depending on the microbial strains from which they are produced and on the production method. Pharmacopeia (EP) dextrans have the following properties:

- Dextran 1 for injection: Low-molecular-weight fraction of dextran, consisting of a mixture of isomaltooligosaccharides. Average relative molecular mass: about 1000).
- Dextran 40 for injection: Mixture of polysaccharides, principally of the α-1,6-glucan type. Average relative molecular mass: about 40 000.
- Dextran 60 for injection: Mixture of polysaccharides, principally of the α-1,6-glucan type. Average relative molecular mass: about 60 000.
- Dextran 70 for injection: Mixture of polysaccharides, principally of the α-1,6-glucan type. Average relative molecular mass: about 60 000.

Dextrans are prepared by hydrolysis and fractionation of sucrose using Leuconostoc mesenteroides strain NRRL B-512 = CIP 78.59 or substrains thereof. They 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

Dextran can be used in medicinal products both as active substance and excipients. As an active substance they can be used to reduce factor VIII-Ag Von Willebrand factor, thereby decreasing platelet function. Low-molecular-weight dextrans (LMWD) are also used during intracoronary imaging, displacing blood during examinations. Larger dextrans (> 60000 Da), 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. They are poorly excreted from the kidney and prolong antithrombotic and colloidal effects.

Dextrans can also be used in pharmaceutical preparations as a lyophilised bulking agent (either parenteral or oral) and as a lyoprotectant in lyophilised protein products. Recently, in the EU, many products containing dextran 40 have been approved in the field of antineoplastic agents. Dextrans are also used in some eye drops as a lubricant, as well as in parenteral preparations to solubilise or transport active ingredients, or as a part of the vector, e.g. iron (= iron dextran). They can also be used as a stabiliser in vaccines, e.g. rotavirus.

Additionally, due to their properties, dextrans have been developed and used as excipients in inhalation products (e.g. Exubera, Rifampicin). Dextrans are biodegradable, neutral, soluble in water and organic solvents; they have good biocompatibility, reduce non-specific protein adsorption and cell attachment; they can be chemically modified to form various structures (spherical, tubular, 3D networks); and as nanoparticles, they exhibit excellent water solubility, high loading capacity, and intrinsic viscosity.

2. Pharmaco-toxicological data

2.1. Toxicology

Dextran (CAS number: 9004-54-0) toxicity after single administration (references: Oyo Yakuri, 1972 [19] and Yakuri to Chiryo, 1975 [22])

Species	**Route**	**LD_{50}**
Mouse	I.V	12 g/kg
Mouse	Oral	> 12.1 g/kg
Mouse	subcutaneous	> 12.1 g/kg
Rat	IV	6.9 g/kg
Rat	oral	> 3 g/kg
Rat	subcutaneous	10.7 g/kg
Rabbit	I.V	208 g/kg
Rabbit	I.V	17.4 g/kg

Dextran 40 toxicity after repeated administration (references: Oyo Yakuri, 1972 [19] and Yakuri to Chiryo, 1975 [22])

Species	Route	Duration	Dose	Observations
Rabbit	I.V	30 days	900 ml/kg/30 d-C	• Liver: Changes in liver weight • Endocrine: changes in adrenal weight • Blood: normocytic anemia
Rabbit	I.V	13 W-I	4680 ml/kg/13W-I	• Liver: Changes in liver weight • Blood: normocytic anemia • Death
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…)

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

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

Ames test (reference: Lubin et al., 1995 [15])

Strain	Dose range (µg/plate)	Metabolic activation	Result
TA98	100-10000	none	negative
TA98	100-10000	rat liver S9	negative
TA100	100-10000	none	negative
TA100	100-10000	rat liver S9	negative
TA100	100-10000	hamster liver S9	negative
TA1535	100-10000	none	negative
TA1535	100-10000	rat liver S9	negative
TA1535	100-10000	hamster liver S9	negative
TA1537	100-10000	none	negative
TA1537	100-10000	rat liver S9	negative
TA1537	100-10000	hamster liver S9	negative
TA1538	100-10000	none	negative
TA1538	100-10000	rat liver S9	negative
TA1538	100-10000	hamster liver S9	negative

Mouse lymphoma TK assay (reference: Seifried et al., 2006 [21])

Cell	Dose range (µg/plate)	Metabolic activation	Result
L5178Y ($tk^{+/-}$)	1000-5000	none	negative
L5178Y ($tk^{+/-}$)	1000-5000	Rat liver S9	negative

Dextran was reported not to induce chromosomal aberrations in cultured Chinese hamster fibroblasts (Ishidate et al., 1978 [10]).

Carcinogenicity

There are no studies conducted on the carcinogenicity of dextrans 40-70. A few studies on the carcinogenicity of dextrans sodium sulfate (DSS) in rats have been performed wherein colon tumors have been observed. However, it should be noted that DSS is a derivative that was specifically developed for experimental models of colitis to induce intestinal toxicity.

Reproductive function toxicity (references: Oyo Yakuri, 1972 [19] and Yakuri to Chiryo, 1975 [23])

There is a lack of data regarding the effects of dextrans on the reproductive and development toxicity.

Product	Species	Route	Sex/Duration	Dose	Observations
Dextran 70	rabbit	I.V	female 8-16 day 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
Dextran 70	rabbit	I.V	male 91-day pre-mating	3640 g/kg/ 91 days LOAEL	• Effects on prostate, seminal vesicle, Cowper's gland, accessory glands

Effects on immune response

Dextrans can activate an immune response from the host after administration. This issue is discussed in more detail in the clinical safety section (see section 4).

2.2. Toxicokinetics

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

3. Pharmacokinetics (in humans)

Several papers have explored the pharmacokinetics of dextran 40 in different patient populations, focusing on the impact of impaired renal function on the elimination of the drug from the body. Kienlen

et al. (1990 [11]) have shown the biexponential decrease in plasma concentrations of dextran 60 after infusion, indicating a linear kinetic pattern with concentration-dependent elimination rates. The distribution of dextran in the vascular and extravascular sectors and the onset of urinary elimination correspond to the first phase of rapid decay, while the second, longer phase corresponds to the elimination of the product, with a half-life of 25.5 ± 7.6 hours. The administration of dextran 60 leads to marked haemodynamic changes, such as haemolysis, hypoproteinemia, urinary hyperviscosity and a decrease in haematocrit. These findings are important for prescribing macromolecular solutions to patients who may experience a sudden decrease in glomerular filtration pressure.

Klotz et al. (1987 [12]) have also studied the pharmacokinetics of dextrans and hydroxyethyl starch, two commonly used plasma volume expanders. The complex composition of these colloidal agents, with a wide distribution of molecular weights in vitro and in vivo, makes their specific determination and pharmacokinetic analysis difficult. The temporal decrease in plasma concentrations of these plasma volume expanders is at least biphasic, with some clinical studies lacking sufficient monitoring periods to characterise the terminal elimination phase.

As reported by Klotz et al. (1987 [12]), elimination rates for dextran 1, 40 and 60 have been shown to be correlated with the size and the molecular weight distribution. For instance, it has been highlighted that dextran 1 has a relatively short elimination half-life of two hours, while dextran 40 and dextran 60 have much longer half-lives of 10 and 42 hours, respectively. Patients with renal impairment require lower doses of dextran, as elimination is altered in parallel with the reduction in glomerular filtration rate. A reduction in dosage may also be necessary in the case of multiple infusions of dextrans, as dextran 40 accumulates considerably with long-term use, particularly in the high molecular weight fractions. As for the metabolism, limited data in humans is available. In rats, 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 in addition to metabolism by dextranases but the depolymerisation process appears to be related to the Mw as expected (Lake et al., 1985 [13]). Low-molecular-weight dextrans (LMWD) 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 molecular-weight dextrans can accumulate in the lymph nodes.

Overall, a molecular weight and dose dependency for tissue accumulation has been shown in animals (Mehvar et al., 1994 [17]; 1995 [16]).

To date, there are no available pharmacokinetic data on the absorption, distribution, metabolism, or elimination of dextrans following pulmonary administration, despite their use as excipients in inhalation products.

4. Clinical safety data

LMWD is a compound used in various medical treatments. Studies have reported cases of acute kidney injuries following its administration, particularly among the elderly and frail individuals. Osmotic nephrosis has been clearly identified as being associated with LMWD. Other theories were explored but refuted. The link between LMWD and osmotic nephrosis was confirmed, especially in patients exposed to large quantities of parenteral solutions (Dickenmann et al., 2008 [4]). However, this type of adverse effect is unexpected with LMWD used as excipient, because of the small quantities of dextran used.

Hypersensitivity / Anaphylactic reaction

A post-authorisation safety study (PASS) was conducted to evaluate the risk of anaphylaxis in patients undergoing intravenous (IV) iron treatment (including both dextran and non-dextran) in Europe from 1999 to 2017. Out of 304,210 first-time IV iron treatments, 13–16 cases of anaphylaxis were reported, with an incidence proportion (IP) of 0.4 to 0.5 per 10,000 treatments. This is in comparison to an IP of 1.2 for penicillin (Fortuny et al., 2021 [7]). The conclusions were restricted due to an inability to distinguish between dextran and non-dextran risks and to account fully for hospital IV iron treatments. The study did bring to light inconsistencies in injectable iron dextran usage across Europe, but also offered reassuring information about IV iron treatment.

In other clinical trials, such as one conducted by Samsudin et al. (2020 [20]), Iron Deficiency Anemia (IDA) during pregnancy was examined. Comparisons were made between Iron Sucrose Complex (ISC) and low-molecular-weight iron dextran (LMWID) administration. Common ISC side effects like diarrhoea, nausea, and dizziness were not found in any of the 20 ISC participants. In contrast, the LMWID group experienced five reactions, including acute anaphylactic reactions, with one individual developing breathlessness. The LMWID group also had significantly higher blood loss, signifying an increase in adverse reactions relative to the ISC group.

There have been reports of anaphylactic shock due to low-molecular-weight dextran (LMWD), although these are rare. While used in intracoronary imaging Dai et al. (2022 [3]) have reported a case of a 70-year-old man with chronic coronary disease who suffered an anaphylactic shock caused by dextran. Following the procedure, his blood pressure suddenly fell to 50 mmHg, and he developed a rash. He was diagnosed with dextran-induced shock and treated with 6 mg of epinephrine, recovering without recurrence 12 days later. These reactions are highly uncommon (0.013% for dextran 40 and 0.025% for dextran 70) but may be lethal. Even minimal amounts of dextran can provoke shock, contingent on molecular size and branching frequency. Such a possibility must be recognised by cardiovascular interventionists when using dextran in intracoronary imaging.

A 2006 pharmacovigilance review study by the United States Food and Drug Administration (FDA) (Zinderman et al., 2006 [24]) scrutinised the frequency and nature of anaphylaxis or anaphylactoid events post clinical dextran administration. Dextrans used in clinic, including dextran 40 and dextran 70, have been associated with anaphylactoid reactions. Despite the known efficacy of pre-treatment of dextran 1 in substantially mitigating these reactions, the FDA noted 366 adverse events between 1969 and 2004, with 24.6% classified as anaphylaxis/anaphylactoid events. Data from hospitals and sales revealed a disproportionate ratio of clinical dextran usage to dextran 1 (28.4:1 and 38.6:1, respectively), a stark deviation from the expected 1:1 ratio if dextran 1 pre-treatment was uniformly applied. This underlines the essential requirement for physicians to habitually use dextran 1 before infusing clinical dextran to decrease the risk of potentially fatal reactions.

The use of epidural analgesia in caesarean sections has led to the practice of preloading the maternal circulation to prevent hypotension, often with dextran solutions. However, the administration of dextrans has been associated with serious risks. A reported case involved a maternal anaphylactoid reaction and apparent neonatal death after administering 100 ml of dextran 40. The infant required immediate resuscitation, followed by seizures. In France, a survey identified 32 similar instances of neonatal disorders linked to dextran use during delivery. This evidence suggests caution in using dextrans (Babier et al., 1992 [2]).

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 et al., 1997 [9]). DIAR are type III immune-complex-mediated anaphylactic reactions that occur when infused dextran molecules bind to endogenous dextran-reactive immunoglobulin (Ig) G antibodies (Neiser et al., 2016 [18]); IgE antibodies are not involved in these type III anaphylactic reactions. Studies have explored the potential of various intravenous iron 40, 70 preparations to induce dextran-induced anaphylactic reactions (DIAR). The dextran antigenicity of several iron preparations was investigated using a mouse anti-dextran monoclonal antibody of IgG isotype and an enzyme-linked immunosorbent assay (ELISA). The results showed that low molecular weight iron dextran, as well as ferumoxytol and dextran-based isomaltoside 1000, reacted with the anti-dextran antibody, whereas ferric carboxymaltose, ferric sucrose, sodium ferric gluconate and isolated isomaltoside 1000 did not. Non-dextran-based preparations, such as iron sucrose and ferric carboxymaltose, do not react with anti-dextran antibodies (Neiser et al., 2016 [18]).

Other publications report that superparamagnetic iron oxide nanoparticles (SPIONs), which are increasingly used in medical imaging applications, some of which are polymer-coated, can cause hypersensitivity reactions (HSR) known as complement activation-related pseudoallergy (CARPA). Only the carboxymethyldextran (ferucarbotran) and dextran (ferumoxtran-10) coated SPIONs caused significant complement activation, while the other coated SPIONs did not. The study also showed that ferumoxtran-10 (Sinerem) was a more potent complement activator than ferucarbotran (Resovist) (Fülöp et al., 2018 [8]).

Furthermore, Laubenthal et al. (1981 [14]) have demonstrated that a decrease in the molecular weight of dextrans has been shown to significantly impact the propensity for reactive immunocomplex formation. By attenuating the molecular weight, the likelihood of immunocomplex formation with anti-dextran antibodies, such as Immunoglobulin G (IgG), has been mitigated. This phenomenon can be exemplified by the utilisation of dextran 1000, which associates with the anti-dextran antibody without resultant immune-complex formation, thereby diminishing the probability of eliciting dextran-induced anaphylactoid reactions (DIARs). Conversely, this attenuation in risk is potentially negated when low molecular weight dextrans are arrayed around a specific nucleus, such as a polynuclear iron core. In the instance of iron isomaltoside 1000 (IIM), where multiple isomaltoside 1000 moieties are appended to a polynuclear iron core, there is a marked enhancement in the formation of reactive immunocomplexes. This intimates that although low molecular weight dextran may be intrinsically less predisposed to immunocomplex formation, its structural organisation around a particular core might reinvigorate this susceptibility (Neiser et al., 2016 [18]).

Hypersensitivity reactions to inhaled formulations containing dextrans, although rare, can be severe. The current clinical safety data, albeit limited, suggest a need for caution when using these agents in patients with a history of allergies or asthma. Monitoring and prior sensitivity testing may be justified to minimise risks.

Orally ingested dextrans are rapidly converted to glucose. According to the opinion of the Scientific committee on food on a dextran preparation (SCCS 2000 [6]) diabetics could be considered as a risk group for bakery products containing significant level of dextrans. However, this is not considered to be a relevant concern when dextrans are used in small amount 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; they have been recognised since the 1960s. Various authors also reported hypersensitivity reactions to dextran used in vaccines as an excipient osmotic agent. 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 for parenteral and inhalation routes of administration. Although those effects are rare, for inhaled products formulated with dextrans, patients with asthma or allergies should be subject to special monitoring. Appropriate treatment should be initiated rapidly when DIAR is suspected.

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