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MINI-REVIEW ARTICLE

Safety of Soluplus® in Pediatrics

Georg Schmitt[1,*]

[1]*Roche Pharma Research and Early Development, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd., Basel 4070, Switzerland*

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Abstract: This paper provides information on the risk and acceptability of the polymeric solubilizer Soluplus® as an excipient in pediatric formulations. The assessment was performed based on safety data available from the manufacturer and publicly available data sources. Soluplus® is virtually non-toxic in rats and dogs after oral administration, consistent with its negligible systemic exposure. The non-toxic dose levels established in animals translate into a substantial Human Equivalent Dose (>300 mg/kg). Clinical safety data in adult subjects further support the presumed safe use of Soluplus® in pediatric clinical formulations. Based on existing data, additional toxicology studies in juvenile animals are not warranted. Overall, the use of Soluplus® as an excipient in pediatric oral clinical formulations in 300 mg or 30 mg/kg can be considered reasonably safe.

Keywords: Soluplus®, excipient, clinical safety, toxicity, pediatrics formulations, clinical formulations.

1. INTRODUCTION

Solubilizers play an important role as absorption enhancers by influencing the permeation of pharmaceutical compounds across membranes. Solubilizing agents such as Kolliphor® EL (formerly Cremophor® EL), polysorbates, and poloxamers are widely used and generally considered safe within established ranges such as applied in several biotherapeutic drug products. Yet, some of these solubilizers can hardly be called innocuous excipients based on their well-known toxicities after intravenous injection. Specific considerations and risks may apply to the pediatric use of solubilizing agents [1].

Soluplus® (CAS number 402932-23-4, chemical name 'Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer') is a graft-copolymer consisting of approximately 13% PEG6000, 57% N-vinyl caprolactam, and 30% vinyl acetate, covalently bonded in the polymer. The average molecular weight of Soluplus® is approximately 115,000 g/mol. Soluplus® possesses physicochemical attributes necessary for improving solubilization, maintaining supersaturation, and preventing the recrystallization of drugs, and is therefore amongst the most extensively used non-ionic amphiphilic copolymers in drug delivery. Soluplus® was particularly developed for solid solutions and has been proposed for many administration routes [2].

Generic applications of oral drug products containing Soluplus® have been approved in several countries, including Argentina, Germany, Poland, the United Kingdom, France, Italy, Slovakia, Romania, Russian Federation and Taiwan. Soluplus® has been used in formulations in many clinical trials in several countries up to high doses. The manufacturer of Soluplus® has initiated the application of a monograph in the European Pharmacopoeia; the publication in Pharmeuropa is expected in the 2nd half of 2022 (the proposed monograph name is "Macrogol Poly (vinyl caprolactam) - poly(vinyl acetate) grafted copolymer"). A subsequent USP-NF monograph is planned. Information on the manufacturing process of Soluplus®, characterization, stability and control in relevance to the product safety is reflected in the US FDA Drug Master File (DMF) Type IV #23504 (containing CMC information) and Type V #23626 (containing safety information) [3, 4].

The present pediatric use assessment of Soluplus® utilizes available non-clinical and clinical safety data and provides information on the risk and acceptability of this relatively novel excipient in formulations when planned for oral administration in pediatric patients. Current non-clinical and clinical guidance dealing with the safety of pediatric formulations are considered.

2. SAFETY DATA FOR SOLUPLUS®

Clinical and non-clinical safety data for Soluplus® are available from the manufacturer [5, 6] and publicly available information sources such as PubMed®.

Clinical data show no particular safety concern for the oral use of Soluplus® in human adults up to high concentration and dose levels. Soluplus® has been used in drug formulations in many clinical trials in several countries (France, Germany, United Kingdom, USA and India). It showed neither local nor systemic intolerability in a total of 70 adult healthy male volunteers following single oral doses up to

*Address correspondence to this author at the Roche Pharma Research and Early Development, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd., Basel 4070, Switzerland; Tel: 0616887576;
E-mail: georg.schmitt@roche.com

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312.5 mg Soluplus® *(i.e.*, about 4.5 mg/kg Soluplus® assuming a body weight of the volunteers of 70 kg) when included as an excipient in tablets containing an active pharmaceutical ingredient. The clinical monitoring included recording adverse events, physical examination up to 72 hours after dosing, recording vital signs and clinical laboratory tests. Another single-dose study in healthy male and female adults (N=8/group) showed no effects on blood pressure, ECGs and laboratory parameters, and no adverse event ascribable to Soluplus® up to an oral dose of 2,000 mg *(i.e.*, 28.6 mg/kg for a human of 70 kg body weight) when included as an excipient in the formulation in a concentration of 80%. The clinical monitoring included a recording of adverse events, clinical observations, vital signs (blood pressure, pulse rate, respiratory rate, body temperature), physical and neurological examination, safety laboratory up to 72 hours after dosing, and electrocardiogram (ECG) assessments up to 12 hours after dosing.

The non-clinical safety of Soluplus® is documented by a comprehensive range of toxicological data in various areas.

General toxicity: GLP-compliant oral studies with Soluplus® in Wistar rats and Beagle dogs up to chronic dosing duration did not reveal target organs of toxicity up to high daily dose levels. In an acute oral toxicity study in rats, a lethal dose (LD50) of greater than 5,000 mg/kg was defined. A No-Observed-Effect Level (NOEL) of 2,000 mg/kg/day was established in a 13-week rat study. A No-Observed-Adverse-Effect Level (NOAEL, except for pseudoallergy) of 1,000 mg/kg/day was defined in a 26-week dog study. These outcomes are consistent with the negligible systemic absorption (<1%) and the resulting insignificant exposure of Soluplus® after oral administration. The vast majority of absorbed Soluplus® is rapidly excreted unchanged in feces (rat and dog data). The pseudoallergy (anaphylactoid reaction) observed in the dog was shown to be histamine-mediated and considered low human relevance based on *in vitro* data suggesting that canine basophils are more susceptible to Soluplus® than human basophils. The non-toxic dose levels of Soluplus® in animals translate into a Human Equivalent Dose (HED) of approximately 320 mg/kg (from rat data: 2,000/6.2) and 550 mg/kg (from dog data: 1,000/1.8), using the HED calculation in the 'Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers' [7]. Applying the 10-fold standard adjustment factor would result in an estimated safe human (starting) dose of approximately 30 mg/kg.

Genotoxicity: Soluplus® was not genotoxic in the standard battery of tests (Ames *in vitro*, mouse lymphoma in vitro, mouse MNT *in vivo*). Even when considering potential genotoxic impurities (such as ethylene oxide or vinyl acetate) possibly present in Soluplus® batches, still considerably high doses of Soluplus® (in the gram range) would be acceptable based on the TTC concept (the intake of a mutagenic impurity of 1.5 µg/person/day is considered to be associated with a negligible risk) [8].

Reproduction toxicity: Soluplus® did not show teratogenic potential (in embryo-fetal toxicity studies in rats and rabbits) and had no adverse effects on fertility endpoints or pre- and postnatal development in rats at oral doses up to the limit dose of 1,000 mg/kg/day.

Safety pharmacology: No adverse effects on safety pharmacology endpoints (central nervous and cardiovascular systems and respiration) were observed in oral repeat-dose toxicity studies in rats and dogs and a dedicated rat plethysmography study up to high dose levels.

Carcinogenicity: Dedicated carcinogenicity studies of Soluplus® were not conducted, and such studies are not considered necessary due to the negligible systemic exposure after oral administration, the negative outcome of the genotoxicity studies, and the lack of any proliferative changes in the repeat-dose toxicity studies conducted in animals up to chronic (26 weeks) duration. According to the US FDA guideline 'Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients [9], no carcinogenicity studies would be warranted for an intermediate use of Soluplus® *(i.e.*, up to 3 months).

Other toxicities: Soluplus® was not irritating to the rabbit's skin or eye, was not sensitizing (Local lymph node assay in the mouse), and did not induce hemolysis in rabbit red blood cells up to high concentration (100 mg/mL).

The overall non-clinical safety package of Soluplus® lacks the following animal studies, typically conducted for the toxicological profiling of chemicals such as pharmaceutical active ingredients and excipients [9]:

1. Safety Pharmacology: CNS screen (Irwin) in the rat; cardiovascular (telemetry) study on the dog. Instead, the manufacturer included in the 90-day rat study a functional observational battery (FOB) and measurement of motor activity. An electrocardiogram recording was performed for several weeks in the chronic dog study.
2. Chronic Toxicology: A 26-week study on the rat; a 39-week study on the dog (for US FDA). Instead, the manufacturer conducted a 26-week dog study. Due to the negligible oral bioavailability of Soluplus® and the absence of adverse findings in the 90-day rat study at a high dose level of 2,000 mg/kg/day, a further 26-week study in rodents was waived.
3. Reproductive toxicology: fertility and early embryonic development study in the rat. The study was waived as fertility and other reproductive parameters were unaffected in the 90-day study and the pre-and postnatal development (PPND) study in rats.
4. Carcinogenicity studies in the rat and the mouse. In a weight-of-evidence approach, the manufacturer did not consider these studies necessary due to negligible systemic absorption, the negative outcome of the genotoxicity studies, and the lack of any proliferative changes in the repeat-dose toxicity studies in rats and dogs.

Based on these rationales (1-4) and scientific considerations, the above studies are deemed not value-adding and thus unnecessary for Soluplus® because the absence of specific risks can be reasonably concluded from already existing data.

The toxicity of excipients can differ between pediatric and adult populations and even across pediatric age groups. Thus, using excipients in pediatric formulations should consider key factors such as age, weight and maturity [10]. Available information on the excipient is evaluated, and a

weight-of-evidence assessment is performed similarly to the procedure for an active ingredient to assess the safety of an excipient in a pediatric clinical formulation [11]. Non-clinical safety studies in juvenile animals with an excipient to support its pediatric use are rarely required and only performed if critically needed for clinical risk assessment and labelling [12]. A weight-of-evidence assessment showed no specific concern for the use of Soluplus® in pediatric populations. Therefore, the conduct of additional juvenile toxicology studies is considered not warranted.

The non-toxic profile and the weight-of-evidence assessment of oral Soluplus® indicate no concern for developing children. The high oral dose levels of Soluplus® tolerated in animal toxicity studies translate into a substantial Human Equivalent Dose (>300 mg/kg). Applying the available data on Soluplus® in the approach generally used for the determination of Acceptable Daily Intakes (ADI, also called Acceptable Daily Exposure (ADE) or Permitted Daily Exposure (PDE), [13]) leads to an extrapolated safe oral human daily dose of about 1 g*. Such ADE values are generally considered conservative enough to also cover children.

*General equation: ADE = NOAEL x Weight Adjustment / F1 x F2 x F3 x F4 x F5

(F1: factor to account for extrapolation between species; F2: factor to account for variability between individuals; F3: factor to account for the duration of the repeat-dose toxicity study; F4: factor to account for the severity of toxicity; F5: factor to account for the point of departure (NOEL, NOAEL, LOEL, LOAEL).

*Equation specific to Soluplus® (using dog data as a conservative starting point):

1,000 mg/kg/day x 50 kg / 2 x 10 x 1 x 1 x 2 = 1,250 mg/day.

CONCLUSION

Current non-clinical and clinical guidelines pertaining to pediatric formulations were considered [7-9]. Calculation of the Acceptable Daily Exposure (ADE) is used as supportive information. The totality of non-clinical and clinical data show no safety concern for the oral use of Soluplus® in human adults up to high doses. In the absence of any specific age-related concern, the use of Soluplus® in pediatric populations at levels (concentrations and doses) already applied in adults *(i.e.*, up to 80% and in the range of 300 mg or 30 mg/kg) is considered reasonably safe and acceptable.

CONSENT FOR PUBLICATION

Not applicable

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CONFLICT OF INTEREST

The author declares no conflict of interest

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