This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Report on Investigation Results

December 12, 2022

Pharmaceuticals and Medical Devices Agency

I. Summary of drug

[Non-proprietary name]	a. Hydroxyethylated starch 130000
	b. Hydroxyethylated starch 70000/sodium chloride/potassium chloride/calcium chloride hydrate/sodium lactate
	c. Hydroxyethylated starch 70000
[Brand name]	a. Voluven 6% solution for infusion
	b. Hespander fluid solution
	c. Salinhes fluid solution 6%
[Marketing authorization holder]	a., b., c. Fresenius Kabi Japan K.K.
[Indications]	a. Maintenance of circulating blood volume
	b., c. Excessive bleeding in various therapeutic areas Haemodilution in extracorporeal circulation
[Dosage and administration]	a. The solution is continuously administered by intravenous infusion. The dose and infusion rate may be adjusted depending on the symptoms of the patients up to 50 mL/kg per day.
	b., c. For adults, the solution is administered by intravenous infusion at a dose of 100 to 1 000 mL. The usual dose for children is less than 10 mL/kg body weight. The dose may be adjusted depending on the symptoms of the patients. Usually, 10 to 20 mL/kg body weight is used for haemodilution in extracorporeal circulation.

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[Investigating office] Office of Pharmacovigilance I

II. Investigation background

Hydroxyethylated starch (hereinafter referred to as “HES”)-containing preparations are blood substitutes that increase the plasma volume based on colloid osmotic effects. In Japan, hydroxyethylated starch 70000 and its combination preparation (hereinafter referred to as “HES70”) were marketed under the brand names of “Hespander fluid solution” and “Salinhes fluid solution 6%” in 1974 and 1987, respectively. In addition, hydroxyethylated starch 130000 (hereinafter referred to as “HES130”) was approved and marketed under the brand name of “Voluven 6% solution for infusion” in March 2013.

In the EU, the safety of HES preparations[1)] was evaluated in 2013 and 2018.

In June 2013, based on the results of overseas clinical studies, etc.,[2)3)4)] the Pharmacovigilance Risk Assessment Committee (hereinafter referred to as “PRAC”) of the European Medicines Agency (hereinafter referred to as “EMA”) concluded that the benefit-risk balance could not be maintained in all indicated patients for the reasons described below, and recommended the suspension of the marketing authorization for HES preparations.

- Increased mortality in patients with sepsis and critically ill patients who received HES preparations
- Increased risk of renal replacement therapy (hereinafter referred to as “RRT”) or renal impairment in patients
- Insufficient data to support the use of HES preparations in patients with burns

Upon the request of the marketing authorization holders (hereinafter referred to as “MAHs”), however, the PRAC conducted a reassessment. It was eventually determined to contraindicate HES preparations in critically ill patients including those with sepsis, patients with burns, and patients admitted to the intensive care unit (hereinafter referred to as “ICU”)

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1) The overseas clinical studies (literature reports 2) to 4) below) that served as the basis for the PRAC's evaluation of the safety of HES preparations in 2013 included clinical studies of HES130 as well as HES200 with different molecular weights.
2) Perner, A. et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med 2012; 367: 124-34.
3) Brunkhorst, F.M. et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med, 2008; 358: 125-39.
4) Myburgh, J.A. et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med 2012; 367: 1901-11.

and to continue the marketing of the preparations, providing that the use of HES preparations should be limited to the treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient, that additional studies would be conducted, and that information would be provided to healthcare professionals and patients.

Among the contraindications listed in the EU Summary of Product Characteristics (hereinafter referred to as "SmPC") for HES preparations, in addition to sepsis, burns, and critically ill patients, severely impaired hepatic function, severe coagulopathy, dehydration, organ transplant patients, and renal impairment or RRT were defined as contraindications based on the PRAC's assessment in 2013. The rationales for the respective contraindications are shown below:

- Severely impaired hepatic function: Details of the rationale are unknown. Severely impaired hepatic function had been listed as a contraindication in the product information before its revision for multiple HES preparations other than HES130.
- Severe coagulopathy: This is defined as a contraindication because clinical studies have shown that HES interacts with the coagulation system, thereby increasing bleeding tendency with both high and low molecular weight HES.
- Dehydration: Details of the rationale are unknown.
- Organ transplant patients: Details of the rationale are unknown.
- Renal failure or RRT: Details of the rationale are unknown. "Renal failure with oliguria or anuria" was listed as a contraindication in the product information before its revision.

In Japan, as of June 2013 when the PRAC recommended the suspension of the marketing authorization for HES130 in the EU, the already approved HES70 was used widely and HES130 was not yet marketed, although marketing authorization had been granted. At the time of the review for its marketing authorization in Japan, HES130 was already widely used overseas, and the "Guidelines for the Use of Anesthetics and Related Drugs" 3rd Edition[5)] also appeared to suggest that HES preparations can be used in patients with sepsis. For these reasons, it was determined to include the precautionary statement that HES130 should be administered only if the therapeutic benefits outweigh the risks because it may exacerbate

5) "Guidelines for the Use of Anesthetics and Related Drugs 3rd Edition: VII Fluid Solutions/Electrolyte Solutions" Japanese Society of Anesthesiologists (2009 to 2010)
For details of description, see Section 3.1. (no revision of the relevant part associated with the revision of the guidelines)

the condition of patients when administered for the management of critically ill patients including those with severe sepsis in the IMPORTANT PRECAUTIONS section in order not to widely encourage the use of HES130 in such patients, although there was no sufficient rationale for contraindicating HES130 in patients with sepsis at the time of review. It was determined to continuously investigate the influence of HES on renal function after marketing. After the PRAC's recommendation for the suspension of the marketing authorization in the EU as of June 2013, a close investigation was conducted in September 2013 in Japan on overseas clinical study results, related literature including meta-analysis reported after the marketing authorization in Japan, and adverse reaction cases reported in Japan and overseas to discuss the necessity of safety measures for HES preparations in view of the clinical significance as plasma substitutes, etc.

For HES130, after confirming the investigation results on overseas clinical studies[2), 4)] at the time of the approval review above, it was considered appropriate to leave the possibility of its use in relative decreased blood volume during the management of critically ill patients including those with severe sepsis under unavoidable circumstances, and a revision was made to the package insert including the following additions:

- A precautionary statement should be added to the WARNINGS section that HES preparations should be administered only if the therapeutic benefits outweigh the risks because it may exacerbate the condition of patients when used in relative decreased blood volume for the management of critically ill patients including those with severe sepsis.
- Renal impairment should be added to the Clinically Significant Adverse Reactions section.
- A precautionary statement should be added to the IMPORTANT PRECAUTIONS section that renal function should be monitored periodically because renal impairment such as acute renal failure may occur and require RRT.
- A statement should be added to the Other Precautions section that it has been reported that the use of HES preparations for fluid management during cardiac surgery using cardiopulmonary bypass in adults was associated with a higher risk of postoperative bleeding requiring blood transfusion and reoperation due to bleeding, compared with the use of albumin, in an overseas clinical study.

The indication for HES70 at the time of the marketing authorization was "excessive

bleeding in various therapeutic areas" and "haemodilution in extracorporeal circulation," and it was not expected to be used in patients with relative decreased blood volume without bleeding. Therefore, without addition of a similar precautionary statement for HES130 to its WARNINGS section, a revision was made to the package insert including the following additions:

- A precautionary statement should be added to the Precautions for Indications section that HES70 should not be used in relative decreased blood volume during the management of critically ill patients including those with severe sepsis.
- A statement should be added to the Clinically Significant Adverse Reactions section that it has been reported that renal impairment such as acute renal failure may occur in similar drugs (HES preparations with different molecular weights or degrees of substitution, etc. from those of this drug).
- The following precautions should be added to the Other Precautions section:
  - In overseas clinical studies, it has been reported that the use of HES preparations in patients with severe sepsis was associated with a higher mortality risk at 90 days after administration and a higher percentage of patients requiring RRT, as compared with the use of Ringer's acetate. It has also been reported that the use of HES preparations in patients admitted to the ICU including those with sepsis was associated with a higher percentage of patients requiring RRT, as compared with the use of saline, although the mortality risk within 90 days after administration did not increase.
  - In an overseas clinical study, it has been reported that the use of HES preparations for fluid management during cardiac surgery using cardiopulmonary bypass in adults was associated with a higher risk of postoperative bleeding requiring blood transfusion and reoperation due to bleeding, compared with the use of albumin.

In 2018, a drug utilization study (hereinafter referred to as "DUS") of HES preparations in the EU revealed continued clinical use of the preparations in critically ill patients, patients with sepsis, patients with impairment, etc. who are contraindicated for the preparations, and the suspension of the marketing authorization was recommended again by the PRAC. Due to their medical needs, however, the European Commission (hereinafter referred to as "EC") decided to continue the marketing of HES preparations, providing that new safety measures

would be taken, including training for healthcare professionals and the supply of preparations only to the medical institutions where trained healthcare professionals were affiliated.

In Japan, considering that these measures taken in the EU were intended to address the non-adherence to instructions for usage and were not due to newly obtained information on concerns about the safety of HES preparations, materials describing the decision on continuation of the marketing in the EU and the request for proper use were prepared and provided to healthcare professionals in 2018, although no issues about non-adherence to instructions for usage have been identified in Japan.

In the EU, continued non-adherence to instructions for usage confirmed in the DUS of HES preparations has resulted in the PRAC's additional recommendation for the suspension of the marketing authorization in February 2022 and the EC's decision on the suspension of the marketing authorization in May 2022. After the discontinuation of the marketing of HES preparations in the EU, the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as "PMDA") conducted an investigation on the safety of HES preparations in Japan pursuant to the provisions of Article 15, Paragraph 1, Item 5 (c) of the Act on the Pharmaceuticals and Medical Devices Agency (Act No. 192 of 2002).

PMDA held an Expert Discussion as part of its investigation. The expert advisors present at the Expert Discussion were nominated based on their conflict of interest declarations concerning the relevant products, pursuant to the "Rules for Convening Expert Discussions, etc., by the Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 20-8, dated December 25, 2008).

III. Outline of investigation by PMDA

1. Current description in the package inserts of HES preparations in Japan and overseas

The indications, dosage and administration, and contraindications described in the package inserts of HES130 and HES70 in Japan and in the package insert of HES130 in the EU, Canada, and Australia are shown in Appendix 1. The indications, dosage and administration, and contraindications described in the package insert of HES130 in France and Germany are the same as those included in the SmPC. HES130 was withdrawn from

the market in the United States and the United Kingdom in 2022 and 2018, respectively, for commercial reasons.

HES70 has not been approved in the United States, the United Kingdom, the EU, Canada, or Australia. In Japan, HES70 is still distributed on the market as of October 2022, although manufacturing was discontinued in September 2020 for commercial reasons.

2. Outline of the drug utilization studies conducted in the EU and the judgment by the EC

In the EU, a DUS was conducted to assess the non-adherence to the indications, contraindications, and dosage and administration described in the approved European product information. The results of the DUS[6)] obtained in 2021 were as shown below:

- Overall, the non-adherence rate for the indications was 18.85% (342/1 814 patients), with the highest non-adherent rates in Belgium (93.3%) and the Netherlands (85.0%) by country. In Belgium, the reasons for non-adherence in 1 of 2 sites were anaesthetic complication (100%) and Caesarean section (71.2%) for the other site. In the Netherlands, the most common reasons for non-adherence were cardiac operation (73.3%) and extracorporeal circulation (73.3%).
- Overall, the non-adherence rate for the contraindications was 6.55% (122/1 863 prescriptions) (3.54% for critically ill patients, 2.20% for renal impairment, 0.97% for sepsis), with the highest non-adherent rates (100%, 57.1%) in 2 sites in Italy. HES130 was used in 18 patients with sepsis (0.97%) (at 10 sites in 6 countries and regions). Of them, 7 had other contraindications in addition to sepsis (renal impairment in 3 patients, severe coagulopathy in 3 patients, severely impaired hepatic function in 2 patients, RRT in 2 patients, dehydration in 1 patient).
- Overall, the non-adherence rate for the dosage and administration was 0.16% (3/1 820 patients).

On the basis of the results of the DUS, the PRAC recommended the suspension of the marketing authorization for HES preparations in February 2022, stating that the benefit-risk

6) Retrospective study conducted in 32 sites accredited for the use of HES130 in 9 countries and regions (Belgium, the Czech Republic, France, Germany, Hungary, Italy, Poland, Spain, the Netherlands). The study included 1 851 patients receiving HES130 between May 2019 and September 2020. The primary endpoint was the number and proportion of patients whose treatment was not in compliance with the approved indications, contraindication, and dosage.

balance of HES preparations could not be maintained, mainly for the reasons shown below, and the EC decided to discontinue the marketing of HES preparations in May 2022:

- The use of HES preparations in contraindicated populations at increased mortality risk raises a significant public health concern.
- Additional safety measures proposed by MAHs, such as further revision of the material for healthcare professionals prepared in 2013 and 2018 and annual training for healthcare professionals are unlikely to exert sufficient effects on non-adherence to the indications, contraindications, and dosage and administration described in the product information in the EU.
- Further risk minimization measures for the safe use of HES preparations, such as revision of the product information and further restriction of use, cannot be identified.
- Even if an additional survey on the status of adherence to the risk minimization measures is conducted, there is a concern that meaningful results will not be obtained because of a limited number of medical institutions that are interested in participating in the DUS. Therefore, it is impossible to confirm proper use.

3. Necessity of additional safety measures for the use of HES preparations in Japan

In Japan, no issues about non-adherence to instructions for usage have been confirmed, as mentioned above, and information has been provided to healthcare professionals through the material regarding the request for proper use prepared in 2018 in response to the measures taken in the EU. It has become recognized that there are multiple populations which are listed as contraindications in the SmPC of HES130 but are not listed as contraindications in the Japanese package inserts. (See Appendix 1.) Therefore, it has been determined to re-confirm the safety of HES preparations in these populations (patients with sepsis, critically ill patients, patients with severely impaired hepatic function, patients with severe coagulopathy, patients with burns, patients with dehydration, organ transplant patients, and patients with renal impairment [7)] (hereinafter referred to as “patients requiring an investigation”) and investigate the necessity of additional safety measures. Since the PRAC’s recommendation to suspend the marketing authorization for HES preparations in

7) The contraindications for patients with renal failure described in the SmPC and the Japanese package inserts are as follows.
SmPC: Renal impairment or renal replacement therapy
Japanese package insert (HES130): Patients with renal failure accompanied by oliguria or anuria, patients on dialysis
Japanese package insert (HES70): Patients with dehydration or renal disorder accompanied by oliguria, etc.

2018, HES130 has been used off-label only in 4 patients (including contraindicated patients) in Japan. Therefore, the MAH states that HES preparations have been used properly in Japan.

Regarding the use of HES preparations in the patients requiring an investigation, the MAH explained the rationale for contraindications in the EU (see "II. Investigation background"), as well as the descriptions in standard textbooks and guidelines in Japan and overseas[8)], the published literature after the PRAC's recommendation for the suspension of marketing in June 2013, and the status of use and adverse reaction reports in Japan, as of May 31, 2022, as described below.

The descriptions in the Japanese package inserts and the SmPC related to the patients requiring an investigation are as shown in Appendix 2.

3.1 Patients with sepsis

(1) Descriptions in standard textbooks and guidelines in Japan and overseas

The following descriptions are included:

[1] Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2020[9)]

Question: Should artificial colloids be used for initial resuscitation in adult patients with sepsis?

Answer: We weakly recommend against administering artificial colloids to patients with

8) The reviewed standard textbooks and guidelines are as follows:
- "Guidelines for Blood Product Use" Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare (2019)
- "Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2020" Japanese Society of Intensive Care Medicine/Japanese Association for Acute Medicine (2020)
- "Clinical Anesthesia Procedures of the Massachusetts General Hospital 7th Edition" translation supervised by Eiichi Inada (2017) Medical Science International, Ltd.
- "New Clinical Anesthesia Standard I General Discussion" edited by Yasuhiro Morimoto, Satoshi Hagihira, Shuya Kiyama, and Tsunehisa Tsubokawa (2020), Kokuseido Co., Ltd.
- "Perioperative Fluid Therapy" edited by Takehiko Iijima (2008), Kokuseido Co., Ltd.
- "Guidelines for the Use of Anesthetics and Related Drugs 3rd Edition 4th Revision: VII Fluid Solutions/Electrolyte Solutions" Japanese Society of Anesthesiologists (2018)
- "Miller's Anesthesia 9th Edition" Gropper, Michael A./Miller, Ronald D./Eriksson, Lars I./Fleisher, Lee A./Wiener-Kronish, Jeanine P./Cohen, Neal H (2019) Elsevier
- "Intravascular volume therapy in adults. Guidelines from the Association of the Scientific Medical Societies in Germany" Marx et al. (2016)
- "Management of severe perioperative bleeding: Guidelines from the European Society of Anesthesiology" Eur J Anaesthesiol 2017; 34: 332–95.

9) "Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2020" Japanese Society of Intensive Care Medicine/Japanese Association for Acute Medicine (2020)

sepsis/septic shock.[10] (Grade 2D): Certainty of evidence = "Very Low"[11]

- Background and importance of this clinical question (CQ)

Determining what fluid to use for initial resuscitation among patients with septic shock is an extremely important problem. However, there is no consensus on whether to use artificial colloids as standard infusion during initial resuscitation. Therefore, it is important to clarify that artificial colloids should be used as standard infusion, and this was taken up as a clinically important issue.

- PICO

P (patients): Adult patients with septic shock requiring initial resuscitation

I (intervention): Use of crystalloids and artificial colloids for initial resuscitation

C (control): Use of crystalloids only without artificial colloids for initial resuscitation

O (outcome): Short-term mortality (28-day or 30-day mortality), long-term mortality (90-day mortality; the longest period should be considered if 90-day mortality is not available), length of ICU stay, serious adverse reaction (dialysis use), serious adverse reaction (serious bleeding)

- Summary of evidence

The results of a systematic review yielded 4 randomized controlled trials (RCT) that conformed to the PICO criteria, and a meta-analysis was performed using these studies.

- Balance between benefits and harms
  - Desired effects: The estimated value (confidence index (CI)) of the effects of short-term mortality outcomes (4 RCTs, n = 2 586) was 9 more per 1 000 patients (25 fewer to 46 more), and the estimated value (CI) of the effects of long-term mortality outcomes (3 RCTs: n = 2 545) was 19 more per 1 000 patients (62 fewer to 123

[10] The recommended strengths specified in the Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock are as shown below. The grading of recommendation was determined by the committee, taking into account the following four factors: Certainty of evidence, balance of effects, values, cost, and resource utilization. The strengths of the recommendations shown in the GRADE system are classified into 4 categories:
- Recommended: Strong recommendation for using an intervention, "We recommend..."
- Suggested: Conditional (weak) recommendation for using an intervention, "We weakly recommend..."
- Not suggested: Conditional (weak) recommendation against using an intervention, "We weakly recommend against..."
- Not recommended: Strong recommendation against using an intervention, "We recommend against..."

[11] Recommendations formulated through discussion by the committee that are presented in accordance with the principles of the GRADE system that takes into account the 4 factors (certainty of evidence, balance between benefits and disadvantages, values and preferences, and utilization of costs/resources), based on the evidence obtained from a systematic review. The definition of the certainty of evidence is as follows:
- High: Highly confident in the estimated value of effects
- Medium: Moderate confidence in the estimated value of effects
- Low: Limited confidence in the estimated value of effects
- Very Low: Almost no confidence in the estimated value of effects

more). The estimated value (CI) of the effects of the outcome of length of ICU stay (2 RCTs; n = 214) was a mean difference (MD) of 1.13 days shorter per 1 000 patients (8.28 shorter to 6.03 longer). Based on the above, it was judged that the desired effects due to artificial colloid administration were trivial.

- Undesired effects: The estimated value (CI) of the effects of outcomes of dialysis use associated with acute kidney injury (hereinafter referred to "AKI") (4 RCTs: n = 3 891) was 16 more per 1 000 patients (24 fewer to 71 more), and the estimated value (CI) of the effects of outcomes of serious bleeding (2 RCTs: n = 994) was 42 more per 1 000 patients (3 more to 97 more). Based on the above, it was judged that the undesired effects of artificial colloid administration were "moderate."
- Balance between benefits and harms: The net balance between benefits and harms was higher for the latter by 86 per 1 000 patients. Even when considering the uncertainty for short-term mortality, using the minimum values of the CI (25 fewer per 1 000 patients), and setting the relative value of outcomes relating to death at 3 times that of the other outcomes, the harm exceeded the benefits by 2 per 1 000 patients. Therefore, the balance of effects was judged such that the "comparative control is likely to superior."

• Certainty of evidence across overall outcomes

The directionality of the estimated value of the effects was inconsistent among the applied outcomes. Therefore, the certainty of the evidence was set as "Very Low," the lowest certainty among the applied outcomes.

[2] Guidelines for the Use of Anesthetics and Related Drugs 3rd Edition 4th Revision: VII Fluid Solutions/Electrolyte Solutions[12)]

Although low-concentration, low-molecular-weight, and low-substituted hydroxyethyl starch preparations have been reported to have less effect, recent studies have reported that renal impairment is caused by solutions with high colloid osmotic pressure, such as 10% hydroxyethyl starch preparations, when used in patients with sepsis.

12) "Guidelines for the Use of Anesthetics and Related Drugs 3rd Edition 4th Revision: VII Fluid Solutions/Electrolyte Solutions" Japanese Society of Anesthesiologists (2018)
https://anesth.or.jp/users/person/guide_line/medicine (only in Japanese)
https://anesth.or.jp/files/pdf/infusion_electrolyte_solution_20190905.pdf (only in Japanese)

[3] Clinical Anesthesia Procedures of the Massachusetts General Hospital 7th Edition[13)]

The use of hydroxyethyl starch in patients with severe sepsis has been associated with an increased mortality and is rarely used at present.

[4] New Clinical Anesthesia Standard I The General Part[14)]

HES preparations should not be used for relative decreased blood volume in patients with severe sepsis.

In pathological conditions with vascular hyperpermeability, use of fluid solutions expected to be retained in the blood vessels for a longer period of time may be advantageous to maintain blood pressure. Colloids are advantageous for volume loading. Because of extravasation of large molecules, however, they also retain water in the interstitium, which causes poor prognosis. It would be better to avoid the use of HES130 in patients with severe sepsis.

[5] Perioperative Fluid Therapy[15)]

What are appropriate fluid solutions in sepsis?

A French study group compared the effects of a HES preparation with a molecular weight of 200 kDa (up to 80 mL/Kg, up to 4 days) on organ function with a gelatin preparation in 129 patients with severe sepsis or septic shock. The group reported a significantly higher incidence of acute renal failure and oliguria in patients receiving HES preparation. A multivariate analysis revealed that use of mechanical ventilation and HES was a risk factor of AKI, and the group recommended that their use should be avoided in patients with severe sepsis or septic shock at risk of acute renal failure. Although the results of this report are not fully agreed upon, they suggest that there are several options of colloids, including long-term continuous administration, which have different effects on individual organ functions.

[6] Intravascular volume therapy in adults. Guidelines from the Association of the Scientific

13) "Clinical Anesthesia Procedures of the Massachusetts General Hospital 7th Edition" translation supervised by Eiichi Inada (2017) Medical Science International, Ltd.
14) "New Clinical Anesthesia Standard I General Discussion" edited by Yasuhiro Morimoto, Satoshi Hagihira, Shuya Kiyama, and Tsunehisa Tsubokawa (2020), Kokuseido Co., Ltd.
15) "Perioperative Fluid Therapy" edited by Takehiko Iijima (2008), Kokuseido Co., Ltd.

Medical Societies in Germany[16)]

Multiple multicenter studies triggered EMA's debate about the benefits and risks of treatment of hypovolaemia in November 2012, and the PRAC advised against the use of HES preparations in patients with sepsis.

[7] Miller's Anesthesia 9th Edition[17)]

In patients with sepsis, even low-molecular-weight HES is associated with an increased risk of bleeding and blood transfusion, but it is unclear whether this also occurs in the perioperative setting.

(2) Published literature

An investigation of published literature on the safety of HES preparations in patients with sepsis using the MEDLINE and Ichushi databases identified 9 literature reports. (See Appendix 4-1 for search conditions.) Investigation results are shown in Appendix 3-1.

There were 5 studies on mortality. Of them, 3 studies reported a significantly high mortality risk for HES preparations and 2 studies reported no significant difference for HES preparations compared with lactated/acetated Ringer's solution. Other than the studies on mortality, 1 study reported a higher incidence of severe AKI or RRT during the first 5 days after the start of administration of HES preparations than acetated Ringer's solution, 1 study reported an increased risk of bleeding for HES preparations, 1 study reported QOL and pruritus with HES preparations, and 1 study reported the status of the use of HES preparations in the United States.

(3) Status of use and adverse reaction reports in Japan

Both the drug use-results survey of HES130 and the spontaneous reports on HES70 and HES130 revealed no use of HES preparations in patients with sepsis.

An investigation of the use status of HES preparations in patients with sepsis in Japan using the Ichushi identified no literature reports on the use of HES preparations in patients with sepsis in Japan. (See Appendix 5-1 for search conditions.)

16) "Intravascular volume therapy in adults. Guidelines from the Association of the Scientific Medical Societies in Germany" Marx et al. (2016)
17) "Miller's Anesthesia 9th Edition" Gropper, Michael A./Miller, Ronald D./Eriksson, Lars I./Fleisher, Lee A./Wiener-Kronish, Jeanine P./Cohen, Neal H (2019) Elsevier

3.2 Critically ill patients

(1) Descriptions in standard textbooks and guidelines in Japan and overseas.

The following descriptions are included:

[1] Guidelines for the Use of Anesthetics and Related Drugs 3rd Edition 4th Revision: VII Fluid Solutions/Electrolyte Solutions[11)]

Indications for colloid fluid/hydroxyethyl starch combined: Relative decreased blood volume during the management of critically ill patients

[2] Clinical Anesthesia Procedures of the Massachusetts General Hospital 7th Edition[9)]

Hydroxyethyl starch is used as an alternative to albumin but may increase the morbidity of complications and mortality in critically ill patients.

[3] Intravascular volume therapy in adults. Guidelines from the Association of the Scientific Medical Societies in Germany[15)]

- As the available multiple studies have offered contradictory results, the Guideline group recommends conducting randomized studies that contrast colloid administration (HES130/gelatin/albumin) with crystalloid administration in critically ill patients.
- In principle, HES should not be used for volume loading in critically ill patients. HES must not be used until the facts have been settled by an investigation as requested. Its use for haemorrhagic shock must be very carefully considered.
- The administration of HES to critically ill ICU patients has been investigated by clinical studies (VISEP, 6S, and CHEST). A correlation was seen between the administration of HES and the risk of RRT initiation. In the 6S study, the administration of HES was associated with increased survival and increased risk of RRT initiation compared to crystalloids. Accordingly, the use of HES in critically ill ICU patients is not recommended. In contrast to the above, one randomized controlled multicenter trial (CRYSTAL) demonstrated a benefit from colloids, including HES, in terms of the 90-day mortality. No significant difference was observed in the primary endpoint of the 28-day mortality.

[4] Miller's Anesthesia 9th Edition[16)]

HES preparations with medium-to-high molecular-weight are associated with oliguria,

increased creatinine, and AKI in critically ill patients with preexisting renal impairment. Although newer solutions with low molecular weight (130 kDa/MS 0.4) were initially thought to be safer in this respect, recent large-scale trials have shown a similar effect on the need for RRT in severe sepsis, particularly when compared with balanced crystalloids. A recent large trial in a mixed critical care population comparing HES with isotonic saline also reported an increase in RRT with the starch solution. This study is more difficult to interpret, given the potential renal effects of saline on kidney, and, as with previous studies, the possibility that patients were given study fluids after partial resuscitation had already been achieved.

(2) Published literature

An investigation of published literature on the outcomes such as death, AKI, or RRT in critically ill patients receiving HES preparations using the MEDLINE and Ichushi databases identified 26 literature reports. (See Appendix 4-2 for search conditions.) Investigation results are shown in Appendix 3-2. There was 1 study (literature No. 1) reporting a significantly high mortality risk in patients with severe sepsis. There were 3 studies (literature No. 1, 2, and 3) reporting a significantly high risk of AKI or RRT initiation: Patient undergoing elective total hip and knee replacement, patient undergoing orthotopic liver transplantation, and patient with severe sepsis. There was another study (literature No. 4) reporting HES as a risk factor for AKI in a trauma patient admitted to the ICU. There were 22 studies (literature No. 5 to 26) investigating death, AKI, or RRT, but they did not show the effect of HES on these outcomes or identify HES as a risk factor for them.

(3) Status of use and adverse reaction reports in Japan

The drug use-results survey of HES130 revealed the use of HES in 1 critically ill patient[*1], who had no adverse reaction. Spontaneous reports revealed the use of HES70 in 1 critically ill patient, who had no adverse reaction[*2], and no use of HES130.

An investigation of the use status of HES preparations in critically ill patients in Japan using Ichushi database identified 1 literature report on the use of HES preparations in a critically ill patient in Japan[18]. (See Appendix 5-2 for search conditions.)

This literature reported an adverse reaction (anaphylaxis) in 1 patient with severe eosinophilic sinusitis receiving HES130.

[18] Yoshiyuki Kyo. Japanese Journal of Rhinology 2018; 57: 121-5.

*1: Patient considered by the reporting physician to be "critically ill" based on the disease names of the primary/underlying disease, complications, and previous diseases
*2: Reported as an adverse event, but not finally considered to be an adverse reaction

3.3 Patients with severely impaired hepatic function

(1) Descriptions in standard textbooks and guidelines in Japan and overseas

There was no description about the use of HES preparations in patients with severely impaired hepatic function.

(2) Published literature

An investigation of published literature on the use of HES preparations in patients with severely impaired hepatic function using the MEDLINE and Ichushi databases identified 2 literature reports. (See Appendix 4-3 for search conditions.) The results are shown in Appendix 3-3. However, both literature reports showed no increased safety risks such as renal disorder or death.

(3) Status of use and adverse reaction reports in Japan

The drug use-results survey of HES130 revealed the use of HES in 15 patients with impaired hepatic function,* none of whom had adverse reactions. Spontaneous reports revealed no use of HES70 or HES130 in patients with impaired hepatic function.

An investigation of the use status of HES preparations in patients with impaired hepatic function in Japan using the Ichushi database identified no literature reports on the use of HES preparations in patients with impaired hepatic function in Japan. (See Appendix 5-3 for search conditions.)

*Patients considered by the reporting physician to be "patients with impaired hepatic function"

3.4 Patients with severe coagulation disorder

(1) Descriptions in standard textbooks and guidelines in Japan and overseas

The following descriptions are included:

Guidelines for the Use of Anesthetics and Related Drugs 3rd Edition 4th Revision: VII Fluid Solutions/Electrolyte Solutions[11)]

Careful administration of colloid fluid/hydroxyethyl starch combined: [1] Patients with bleeding tendency, [2] patients with a history of hypersensitivity such as rash

(2) Published literature

An investigation of published literature on the use of HES preparations in patients with severe coagulation disorder using the MEDLINE and Ichushi databases identified no literature reports. (See Appendix 4-4 for search conditions.)

(3) Status of use and adverse reaction reports in Japan

The drug use-results survey of HES130 revealed the use of HES in 1 patient with coagulation disorder, who had no adverse reaction. Spontaneous reports revealed no use of HES70 or HES130 in patients with coagulation disorder.

An investigation of the use status of HES preparations in patients with coagulation disorder in Japan using the Ichushi database identified no literature reports on the use of HES preparations in patients with coagulation disorder in Japan. (See Appendix 5-4 for search conditions.)

3.5 Patients with burns

(1) Descriptions in standard textbooks and guidelines in Japan and overseas

The following descriptions are included:

Intravascular volume therapy in adults. Guidelines from the Association of the Scientific Medical Societies in Germany[15)]

Multiple multicenter studies triggered EMA's debate about the benefits and risks of treatment of hypovolaemia in November 2012, and the PRAC advised against the use of HES preparations in patients with burns.

(2) Published literature

An investigation of published literature on the use of HES preparations in patients with burns using the MEDLINE and Ichushi databases identified 2 literature reports. (See Appendix 4-5 for search conditions.) The results are shown in Appendix 3-4.

Both studies investigated the effects of HES preparations on renal disorder or death in patients with burns, but showed no significant increase in the risk.

(3) Status of use and adverse reaction reports in Japan

The drug use-results survey of HES130 revealed the use of HES in 1 patient with burns,

who had no adverse reaction. Spontaneous reports revealed no use of HES70 or HES130 in patients with burns.

An investigation of the use status of HES preparations in patients with burns in Japan using the Ichushi database identified no literature reports on the use of HES preparations in patients with burns in Japan. (See Appendix 5-5 for search conditions.)

3.6 Patients with dehydration

(1) Descriptions in standard textbooks and guidelines in Japan and overseas

There was no description about the use of HES preparations in patients with dehydration.

(2) Published literature

An investigation of published literature on the use of HES preparations in patients with dehydration using the MEDLINE and Ichushi databases identified no literature reports. (See Appendix 4-6 for search conditions.)

(3) Status of use and adverse reaction reports in Japan

The drug use-results survey of HES130 revealed the use of HES in 4 patients with dehydration, none of whom had adverse reactions. Spontaneous reports revealed no use of HES70 or HES130 in patients with dehydration.

An investigation of the use status of HES preparations in patients with dehydration in Japan using the Ichushi database identified no literature reports on the use of HES preparations in patients with dehydration in Japan. (See Appendix 5-6 for search conditions.)

3.7 Organ transplant patients

(1) Descriptions in standard textbooks and guidelines in Japan and overseas

There was no description about the use of HES preparations in organ transplant patients.

(2) Published literature

An investigation of published literature on the use of HES preparations in organ transplant patients using the MEDLINE and Ichushi databases identified 5 literature reports. (See Appendix 4-7 for search conditions.) The results are shown in Appendix 3-5.

The 5 literature reports included 1 study reporting a significantly increased incidence of

AKI with HES administration in patients undergoing orthotopic liver transplantation, 1 study reporting significantly higher use of HES preparations during lung transplantation in patients who died during follow-up versus those who survived, and 2 studies reporting HES as a risk factor of AKI in patients undergoing heart or lung transplantation. The remaining 1 study reported no increase in the safety risk such as renal disorder or death with HES as compared to gelatin (control).

(3) Status of use and adverse reaction reports in Japan

The drug use-results survey of HES130 revealed that no cases of adverse reactions occurred after HES was administered to organ transplant patients. Spontaneous reports also revealed no use of HES70 or HES130 in organ transplant patients.

An investigation of the use status of HES preparations in organ transplant patients in Japan using the Ichushi database identified no literature reports on the use of HES preparations in organ transplant patients in Japan. (See Appendix 5-7 for search conditions.)

3.8 Patients with renal failure

(1) Descriptions in standard textbooks and guidelines in Japan and overseas

The following descriptions are included:

[1] Guidelines for the Use of Anesthetics and Related Drugs 3rd Edition 4th Revision: VII Fluid Solutions/Electrolyte Solutions[11)]

Contraindications for colloid fluid/hydroxyethyl starch combined: [1] Patients with congestive cardiac failure, [2] Patients with dehydration or renal disorder with oliguria, etc.

[2] Clinical Anesthesia Procedures of the Massachusetts General Hospital 7th Edition[12)]

The use of hydroxyethyl starch in patients with renal failure has been associated with an increased mortality and is rarely used at present.

(2) Published literature

An investigation of published literature on the use of HES preparations in patients with renal failure using the MEDLINE and Ichushi databases identified no literature reports. (See Appendix 4-8 for search conditions.)

(3) Status of use and adverse reaction reports in Japan

The drug use-results survey of HES130 revealed the use of HES in 16 patients with renal impairment, none of whom had adverse reactions. According to spontaneous reports, HES70 was used in 2 patients with renal impairment (1 with nephrotic syndrome and 1 with renal failure) and adverse reactions were reported in 2 patients (increased brain natriuretic peptide and decreased haemoglobin in 1 patient and AKI in 1 patient). HES130 was used in 3 patients with renal impairment (2 with renal failure and 1 on dialysis) and adverse reactions were reported in 1 patient (renal failure).

An investigation of the use status of HES preparations in patients with renal impairment in Japan using the Ichushi database identified 1 literature report on the use of HES preparations in a patient with impaired renal function in Japan[19]. (See Appendix 5-8 for search conditions.)

This literature reported no adverse reaction in patients with renal failure receiving HES130.

IV. PMDA's judgment based on the investigation results

Necessity of additional safety measures for the patients requiring investigation

PMDA concluded that it is appropriate to revise the package inserts of HES130 and HES70, as shown in Appendix 6, to contraindicate the administration of HES in patients with sepsis for the reasons described below.

1. Patients with sepsis

In the Japanese package insert of HES130, the "WARNINGS" section currently states as follows: "The condition of patients may be exacerbated when this drug is used in relative decreased blood volume during the management of critically ill patients. This drug should be administered only if the therapeutic benefits outweigh the risks."

However, based on the mortality risk reported in the literature after the review in 2013 and the descriptions in standard textbooks and guidelines in Japan and overseas, it was determined to contraindicate HES in patients with sepsis in the Japanese package inserts as well. To date, no patients with sepsis given HES130 have been confirmed in its drug use-results survey or spontaneous reports in Japan.

Although use of HES70 in patients with sepsis is not usually expected based on the indications approved for marketing, its use is covered by the indications in the case of major

[19] Shunsuke Tachibana. Hakodate Medical Journal 2014; 38: 33-34.

bleeding suggesting absolute decreased blood volume. However, even when HES is administered to patients with sepsis accompanied by major bleeding, it is considered that restoration of circulating blood volume cannot be expected due to peripheral vascular hyperpermeability and that renal function may be exacerbated by HES. Based on the above, in addition to the reason for contraindicating HES130, it is appropriate to contraindicate HES70 in patients with sepsis, as with HES130. Spontaneous reports on HES70 in Japan revealed no use in patients with sepsis.

2. Critically ill patients

In the Japanese package insert of HES130, the “WARNINGS” section states as follows: “The condition of patients may be exacerbated when this drug is used in relative decreased blood volume during the management of critically ill patients. This drug should be administered only if the therapeutic benefits outweigh the risks.” In the Japanese package insert of HES70, the “PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION” section states that “This drug should not be used in relative decreased blood volume during the management of critically ill patients including those with severe sepsis.” Literature on the outcomes such as death, AKI, or RRT in critically ill patients published after the review in 2013 was investigated. According to the investigation, for critically ill patients other than those with sepsis, there was no report on confirmed increased mortality risk and there were reports on increased risk of AKI or RRT initiation. However, populations of critically ill patients varied in each study, and some reports showed no increased risk of AKI or RRT initiation, indicating inconsistent results of the studies.

Therefore, there is no sufficient basis for newly contraindicating HES preparations in all critically ill patients or in specific critically ill patients. Both the drug use-results survey of HES130 and the literature in Japan revealed the use of HES in 1 critically ill patient, and it was confirmed that these patients had no adverse reaction.

Based on the above, it is currently considered that there is little need to take additional safety measures for both HES130 and HES70 in critically ill patients.

3. Other patients requiring investigation

No reports on the increased risk of death, etc. with HES preparations in the patients requiring an investigation, other than patients with sepsis and critically ill patients, could be

identified, or results were inconsistent among reports. In Japan, no adverse reactions have been reported in the patients requiring an investigation other than patients with sepsis and critically ill patients, except for 3 patients with renal failure receiving HES in adverse reaction reports. Therefore, it is considered that there is no particular concern in Japan about the administration of HES in these patients requiring an investigation and that the necessity to take additional safety measures against HES130 and HES70 is not high at present.

V. Expert discussion (1)

Necessity of additional safety measures for the patients requiring investigation

1. Patients with sepsis

PMDA decided that it is appropriate to contraindicate administration of HES preparations to patients with sepsis in the package inserts of HES130 and HES70. The decision was generally supported by the expert advisors; however, the following opinions were expressed by the expert advisors.

- Regarding the risk with the administration of HES preparations to patients with sepsis, opinions may differ among specialists as to whether or not it is appropriate to contraindicate the administration of HES preparations to patients with sepsis.
- From an epidemiological perspective, there may not be a strong enough rationale for contraindicating the administration of HES preparations to patients with sepsis.
- Emergency transfusion is basically indicated for patients with sepsis considered to have absolute decreased blood volume due to major bleeding. However, administration of HES preparations may be necessary to maintain circulation in situations where it is impossible to adequately prepare for transfusion for recovery from an emergency status or for resuscitation, or in some institutions.
- There is still a lack of evidence on the balance between the benefits and harms of the administration of HES preparations, warranting a further investigation.

2. Patients requiring investigation other than patients with sepsis

PMDA decided that there is little need to take additional safety measures for the patients requiring an investigation, including critically ill patients, other than patients with sepsis, and the decision was supported by the expert advisors.

VI. View of the related academic society and PMDA's judgment based on the view

Taking into account the expert advisors' opinions (see "V. 1. Patients with sepsis"), PMDA requested a view from the Japanese Society of Intensive Care Medicine, which published the Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2020,[9] about the appropriateness of contraindicating administration of HES preparations to "patients with sepsis" in the package inserts of HES130 and HES70.

1. Patients with sepsis

The Japanese Society of Intensive Care Medicine commented that the target patient population for precautions should be limited by contraindicating the administration of HES preparations to patients with "severe sepsis," "sepsis accompanied by severe organ dysfunction," etc. for the following reasons (Appendix 8). (Appendix 8 is not included in this document. See the Japanese original report.)

- The target patient populations in the overseas clinical studies evaluating the risk with the administration of HES preparations are patients with severe sepsis and ICU patients including those with sepsis.
- The potential risk in the target patient populations in the overseas clinical studies above has not been confirmed in sepsis patients with mild organ dysfunction.

Based on the above view from the Japanese Society of Intensive Care Medicine, PMDA decided that it is appropriate that "patients with severe sepsis" should be added to the "CONTRAINDICATION" section and "patients with sepsis (excluding patients with severe sepsis)" to the "Careful Administration" section and that information about the target patient populations should be provided as a reference regarding the overseas clinical studies, which are already described in the "Other Precautions" section, for the following reasons.

- The target patient populations in the overseas clinical studies evaluating the risk with the administration of HES preparations,[2),4)] which are also cited in the current package inserts, are patients with severe sepsis[20)] and ICU patients including those with sepsis.

[20)] Severe sepsis is defined as follows:
Sepsis* with at least one organ dysfunction (= SOFA score >2) (except when organ dysfunction is already present 48 hours before the onset of sepsis)
*Sepsis: both (i) and (ii) below are met:
(i) Infection confirmed by the presence of microorganisms grown in the blood or sterile areas, or infection confirmed by the presence of an abscess or infected tissue (e.g. pneumonia, peritonitis, urinary tract, vascular line infection, soft tissue)
(ii) Systemic inflammatory response syndrome (SIRS) criteria are met**

- The major patient population in clinical studies currently showing the risk with the administration of HES preparations is patients with severe sepsis, and the risk with HES preparations in other patients with sepsis is currently unknown.
- With the changes over time in the Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock, the definition of sepsis was changed from "systemic inflammatory response syndrome (SIRS) caused by infection" to "a condition in which serious organ dysfunction is caused by infection" in the 2016 version,[21)] and the definition of "severe sepsis" has been deleted thereafter. Therefore, regarding the term "severe sepsis" used in the current package inserts, it is considered inappropriate to specify patients with "severe sepsis" as the patients to whom administration of HES preparations is contraindicated.

  (Note: The change of the terms for "severe sepsis" in Japanese language above does not affect the context of this English version of the documents since both the new and old Japanese terms are translated as "severe sepsis" and are unchanged.)
- The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2020[9)] state as follows, "Sepsis is a pathological condition showing a great diversity depending on its cause, severity, stage, comorbidities, complications, etc. In the clinical settings, clinician's decisions must be made on an individual patient basis, taking into account not only the patient's condition, but also the availability and resources of healthcare professionals and the wishes of the patient and family or caregivers." It is therefore considered that the severity of sepsis should be judged appropriately in clinical settings not only by the sequential (sepsis-related) organ failure assessment (SOFA) score and the quick SOFA (qSOFA) score, which are recommended in the current guidelines.

**SIRS: at least two of the following criteria are met:
(1) Body temperature >38°C or <36°C (to be measured in the rectum, bladder, central line, or tympanic membrane). If oral, groin, or axillary temperature is used, add 0.5°C to the measured value. Hypothermia <36°C should be confirmed only in the rectum, bladder, central line, or tympanic membrane. Use the temperature that is of the most concern recorded during the 24 hours before randomization.
(2) Heart rate ≥90 beats per minute. If atrial arrhythmia is present, record the ventricular heart rate. Any patient who has known symptoms or is receiving treatment to prevent tachycardia (e.g. heart block, beta blockers) should meet 2 of the remaining 3 SIRS criteria. Use the heart rate that is of the most concern recorded during the 24 hours before randomization.
(3) Respiratory rate >20 breaths/min, $PaCO_2$ <4.3 kPa (32 mmHg), or mechanical ventilation in the acute phase. Use the worst respiratory rate or $PaCO_2$ value recorded during the 24 hours before randomization.
(4) White blood cell count ≥12 × 10^9/L or <4 × 10^9/L, or immature neutrophils (band form) ≥10%. Use the worst value recorded during the 24 hours before randomization.

21) Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2016, Japanese Society of Intensive Care Medicine/Japanese Association for Acute Medicine (2016)

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- The major published literature on the risk with the administration of HES to patients with sepsis includes the overseas clinical studies,[2)] which are cited in the current package inserts, and 3 publications after the PRAC's recommendation in 2013 reporting the effect of HES on the mortality risk in patients with sepsis. (See "III. 3.1 (2) Published literature.") Of the 3 publications after the PRAC's recommendation in 2013 reporting the effect of HES on the mortality risk in patients with sepsis, 2 are systematic reviews and 1 is a study in patients with shock in which the definition of sepsis was not clearly described. Therefore, the overseas clinical studies,[2)] which are cited in the current package inserts, may be most helpful in identifying "patients with severe sepsis" in clinical settings, to whom administration of HES preparations is to be contraindicated. Thus, it was considered appropriate to include in the package inserts the information on the target patient populations in the clinical studies.

2. Patients other than sepsis patients

The Japanese Society of Intensive Care Medicine answered that the necessity is not high to take additional safety measures for patients other than those with sepsis at present when it was asked about the necessity to include additional safety measures in the package inserts of HES130 and HES70 (Appendix 8).

VII. Expert discussion (2)

PMDA decided that it is appropriate that "patients with severe sepsis" should be added to the "CONTRAINDICATION" section and "patients with sepsis (excluding those with severe sepsis)" to the "Careful Administration" section in the package inserts of HES130 and HES70 and that information about the target patient populations should be provided as a reference regarding the overseas clinical studies, which are already cited in the "Other Precautions" section. (See "VI. 1. Patients with sepsis.") The decision was supported by the expert advisors.

VIII. Outline of additional investigation by PMDA

Concerning the MAH's explanation that "HES preparations have been used properly in Japan" (See "III. 3. Necessity of additional safety measures for the use of HES preparations in Japan."), PMDA confirmed the status of use of HES preparations in Japan as described

below, concluding that it is not necessary to limit the current usage in Japan, unlike that in the EU (See "III. 2. Outline of the drug utilization studies conducted in the EU and the judgment by the EC."), although further promotion of the proper use of HES preparations is needed, taking into account their needs and usage in the clinical settings. In addition, the Japanese Society of Intensive Care Medicine, the related academic society, commented that no usage conditions had been confirmed that would require safety measures in Japan (Appendix 8).

- In a drug use-results survey of HES130 (in a total of 1 390 patients), there was no case of off-label use.[22] However, it was found that the preparations had been administered to 16 patients to whom administration is contraindicated (1 patient with fluid overload [congestive cardiac failure], 6 patients with renal failure,[23] 9 patients on dialysis) and had been administered outside the approved dosage[24] to 9 patients (including 1 of the 6 patients with renal failure above). None of these 16 patients reported any adverse drug reaction.
- According to spontaneous reports, HES130 was used off-label[25] in 3 patients (1 patient with unknown reason for use, 1 patient with sudden hearing loss, 1 patient with intravascular dehydration) and HES70 was used off-label in 1 patient (administration to maintain urine volume). HES130 was administered to 3 patients to whom administration is contraindicated (2 patients with renal failure,[21] 1 patient on dialysis) and HES70 to 2 patients to whom administration is contraindicated (2 patients with renal failure[21]). HES130 was administered beyond the approved dosage[26] to 2 patients, but there was no patient to whom HES70 was administered beyond the approved dosage. No adverse drug reactions were reported with off-label use. However, adverse drug reactions were reported in 1 patient to whom administration of HES130 is contraindicated,[27] 2 patients to whom administration of HES70 is contraindicated,[28] and 1 patient to whom the

[22] Patients whose "Reason for administration of the product" in the registration form of use-results survey is "Other"
[23] Unclear whether the patients correspond to the contraindicated patients in the package insert in Japan because of no information on the presence or absence of oliguria or anuria
[24] Patients extracted as "Patients receiving a dose exceeding 50 mL/kg/day" based on analysis results
[25] Patients reported as "Off label use" or "Intentional product misuse" (MedDRA PT)
[26] Patients reported as "Overdose" or "Intentional product misuse" (MedDRA PT), patients found to have received >50 mL/kg of HES130 based on their clinical courses, or patients found to have received >1000 mL of HES70 (for excessive bleeding in various therapeutic areas) or >20 mg/kg (for haemodilution in extracorporeal circulation) despite the dosage instruction, "The dose may be adjusted depending on the symptoms of the patients."
[27] Renal failure
[28] 1 patient with increased brain natriuretic peptide and haemoglobinaemia, 1 patient with acute renal failure

preparation was administered beyond the approved dosage.[29)]

IX. Overall evaluation

Taking into account "V. Expert discussion (1)," "VI. Views of the related academic society and PMDA's judgment based on the view," "VII. Expert discussion (2)," and "VIII. Outline of additional investigation by PMDA," PMDA concluded that it is appropriate to revise the Precautions in the draft revision of the package insert (Appendix 6) to add "patients with severe sepsis" in the CONTRAINDICATIONS section and "patients with sepsis (excluding patients with severe sepsis)" to the "Careful Administration" section as shown in Appendix 7. (Appendix 7 is not included in this document. See the Detailed information on revisions of PRECAUTIONS.) In addition, PMDA concluded that the necessity is low to take additional safety measures for the proper use of HES preparations in Japan and for the safety in the patients requiring an investigation other than patients with sepsis.

[29)] Patient with renal impairment

Appendix 1

Descriptions of indications, dosage and administration, and contraindications in package inserts in Japan and overseas

	Japan HES70 (Hespander fluid solution, Salinhes fluid solution 6%)	Japan HES130 (Voluven 6% solution for infusion)	EU (SmPC) HES130 (Voluven Fresenius 6% solution for infusion)
Indications	Excessive bleeding in various therapeutic areas Haemodilution in extracorporeal circulation	Maintenance of circulating blood volume	Treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient
Dosage and administration	For adults, the solution is administered by intravenous infusion at a dose of 100 to 1 000 mL. The usual dose for children is 10 mL or less/kg body weight. The dose may be adjusted depending on the symptoms of the patients. Usually, 10 to 20 mL/kg body weight is used for haemodilution in extracorporeal circulation.	The solution is continuously administered by intravenous infusion. The dose and infusion rate may be adjusted depending on the symptoms of the patients up to 50 mL/kg per day.	For intravenous use as infusion. Use of HES should be restricted to the initial phase of volume resuscitation with a maximum time interval of 24 h. The first 10-20 mL should be infused slowly and under careful monitoring of the patient so that any anaphylactic/anaphylactoid reaction can be detected as early as possible. The daily dose and rate of infusion depend on the patient's blood loss, on the maintenance or restoration of haemodynamics and on the haemodilution (dilution effect). The maximum daily dose is 30 mL/kg for Voluven Fresenius 6%. The lowest possible effective dose should be applied. Treatment should

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	Japan HES70 (Hespander fluid solution, Salinhes fluid solution 6%)	Japan HES130 (Voluven 6% solution for infusion)	EU (SmPC) HES130 (Voluven Fresenius 6% solution for infusion)
			be guided by continuous haemodynamic monitoring so that the infusion is stopped as soon as appropriate haemodynamic goals have been achieved. The maximum recommended daily dose must not be exceeded. Paediatric population: Data are limited in children, therefore it is recommended not to use HES products in this population.
Contraindications	1. Patients with congestive cardiac failure [Congestive cardiac failure may be exacerbated since this drug increases circulating blood volume.] 2. Patients with dehydration or renal disorder accompanied by oliguria, etc. [Renal failure may occur.] 3. Patients with a history of hypersensitivity such as rash to this drug or its ingredients	1. Patients with fluid overload including pulmonary oedema and congestive cardiac failure [Symptoms may be exacerbated since this drug increases circulating blood volume.] 2. Patients with renal failure accompanied by oliguria or anuria [Excretion of this drug may be delayed in patients with renal failure.] 3. Patients on dialysis [Excretion of this drug may be delayed.] 4. Patients with intracranial haemorrhage [intracranial haemorrhage may be exacerbated.] 5. Patients with severe hypernatraemia	- Hypersensitivity to the active substances or to any of the other excipients listed in section 6.1 - Sepsis - Burns - Renal impairment or renal replacement therapy - Intracranial or cerebral haemorrhage - Critically ill patients (typically admitted to the intensive care unit) - Hyperhydration - Pulmonary oedema - Dehydration - Severe hypernatraemia or severe hyperchloraemia

	Japan HES70 (Hespander fluid solution, Salinhes fluid solution 6%)	Japan HES130 (Voluven 6% solution for infusion)	EU (SmPC) HES130 (Voluven Fresenius 6% solution for infusion)
		or severe hyperchloraemia [Symptoms may be exacerbated since this drug contains sodium chloride.] 6. Patients with a history of hypersensitivity to this drug or its ingredients	- Severely impaired hepatic function - Congestive heart failure - Severe coagulopathy - Organ transplant patients

	Canada HES130 (Voluven)	Australia HES130 (Voluven)
Indications	Voluven is indicated for the treatment of hypovolemia due to acute blood loss when crystalloids alone are not considered sufficient. Voluven is not a substitute for red blood cells or coagulation factors in plasma.	Treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient. The use of Voluven is not a substitute for the appropriate use of packed red blood cells or fresh frozen plasma.
Dosage and administration	Voluven (6% HES 130/0.4 in 0.9% sodium chloride injection) is administered by intravenous infusion only. Total volume and rate of infusion are dependent on the clinical situation and the individual patient. As with any intravenous fluid, Voluven should be administered in accordance with accepted clinical practices for fluid and electrolyte management. In clinical trials, infusions up to 33 mL/kg/day were most commonly used. There is limited experience with infusions between 33 mL/kg/day and 50 mL/kg/day. The initial 10-20 mL is to be infused slowly, keeping the patient under close observation for possible anaphylactic/anaphylactoid reactions. Voluven can be administered repetitively over several days according to the patient's needs. The dosage and duration of treatment depends on the duration and extent of hypovolemia, the hemodynamics and on the hemodilution. Children: Data are limited in children, therefore it is not recommended to use HES products in this population	For intravenous infusion. Use of Voluven should be restricted to the initial phase of volume resuscitation with a maximum duration of use of 24 hours. Administration of Voluven may cause anaphylactic reactions that may manifest as acute hypotension. In all patients, the initial 10-20 mL of Voluven should be infused slowly, keeping the patient under close observation for anaphylactic/anaphylactoid reactions manifesting as unexpected hypotension, or the development of wheeze or rash. The daily dose and rate of infusion depend on the patient's blood loss, on the maintenance or restoration of haemodynamics and on the haemodilution (dilution effect).

	Canada HES130 (Voluven)	Australia HES130 (Voluven)
Contraindications	Voluven is contraindicated in patients: ➢ with fluid overload (hyperhydration), especially in cases of pulmonary edema and congestive cardiac failure. ➢ with sepsis. ➢ with renal impairment with oliguria or anuria not related to hypovolemia. ➢ with critical illness (typically admitted to the intensive care unit). ➢ with severe liver disease. ➢ receiving dialysis treatment. ➢ with severe hypernatremia or severe hyperchloremia. ➢ with known hypersensitivity to hydroxyethyl starch. ➢ with intracranial bleeding. ➢ with pre-existing coagulation or bleeding disorders.	Voluven should not be used, if any one or more of the following clinical conditions apply: · Critically ill patients (typically admitted to intensive care unit), including those with sepsis · Fluid overload (hyperhydration), especially in cases of pulmonary oedema and congestive cardiac failure · Patients with pre-existing coagulation or bleeding disorders · Renal failure with oliguria or anuria not related to hypovolaemia · Patients receiving dialysis treatment · Intracranial bleeding · Severe hypernatraemia or severe hyperchloraemia · Known hypersensitivity to hydroxyethyl starches · Patients with severe liver disease

This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Appendix 2

Descriptions concerning patients requiring investigation in package inserts in Japan and overseas

<table>
<tr><th></th><th>Japan
HES70 (Hespander fluid solution, Salinhes fluid solution 6%)</th><th>Japan
HES130 (Voluven 6% solution for infusion)</th><th>EU (SmPC)
HES130</th></tr>
<tr><td>Sepsis</td><td rowspan="2">Precautions Concerning Indications
This drug should not be used in relative decreased blood volume during the management of critically ill patients including those with severe sepsis.

Other Precautions
In overseas clinical studies, it has been reported that the use of HES preparations note) in patients with severe sepsis was associated with a higher mortality risk at 90 days after administration and a higher percentage of patients requiring renal replacement therapy, as compared with the use of acetated Ringer’s solution. It has been also reported that the use of HES preparations in patients admitted to the ICU including patients with sepsis was associated with a higher percentage of patients</td><td rowspan="2">Warnings
The condition of patients may be exacerbated when this drug is used in relative decreased blood volume during the management of critically ill patients including patients with severe sepsis. This drug should be administered only if the therapeutic benefits outweigh the risks.

Other Precautions
In overseas clinical studies, it has been reported that the use of HES preparations in patients with severe sepsis was associated with a higher mortality risk at 90 days after administration and a higher percentage of patients requiring renal replacement therapy, as compared with the use of acetated Ringer’s solution.
It has been also reported that the use</td><td>Contraindications
- Sepsis</td></tr>
<tr><td>Critically ill patients</td><td>Contraindications
- Critically ill patients (typically admitted to the intensive care unit)</td></tr>
</table>

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	Japan HES70 (Hespander fluid solution, Salinhes fluid solution 6%)	Japan HES130 (Voluven 6% solution for infusion)	EU (SmPC) HES130
	requiring renal replacement therapy, as compared with the use of normal saline, although the mortality risk up to 90 days after administration did not increase. Note) HES preparations with different molecular weights or degrees of substitution, etc. from those of this drug	of HES preparations in patients admitted to the ICU including patients with sepsis was associated with a higher percentage of patients requiring renal replacement therapy, as compared with the use of normal saline, although the mortality risk up to 90 days after administration did not increase.	
Severe hepatic impairment	(No description)	(No description)	Contraindications - Severely impaired hepatic function Undesirable effects *Hepatobiliary disorders* Frequency not known (cannot be estimated from the available data): Hepatic injury.
Severe coagulation disorder	Relative Contraindications Patients with fibrinogenopenia or bleeding tendency including	Careful Administration Patients with haemorrhagic diathesis [Bleeding tendency may be	Contraindications - Severe coagulopathy Undesirable effects

	Japan HES70 (Hespander fluid solution, Salinhes fluid solution 6%)	Japan HES130 (Voluven 6% solution for infusion)	EU (SmPC) HES130
	thrombocytopenia [Administration at a high dose may enhance bleeding tendency.] Other Adverse Reactions Prolonged bleeding time, bleeding tendency Other Precautions In an overseas clinical study, it has been reported that the use of HES preparations note) for fluid management during cardiac surgery using cardiopulmonary bypass in adults was associated with a higher risk of postoperative bleeding requiring blood transfusion and reoperation due to bleeding, as compared with the use of albumin. Note) HES preparations with different molecular weights or degrees of substitution, etc. from those of this drug	enhanced.] Important Precautions Administration of this drug at a high dose may cause dilution of blood components such as coagulation factors and other plasma proteins. In addition, coagulation disorder not solely due to dilution of blood components may occur. The dose of this drug should be adjusted depending on the conditions of the patients, and appropriate measures should be taken such as administration of blood preparations as necessary. Other Adverse Reactions Prolonged activated partial thromboplastin time, prolonged prothrombin time, post procedural haemorrhage, wound haemorrhage	*Blood and lymphatic system disorders* Rare (in high doses): With the administration of hydroxyethyl starch disturbances of blood coagulation can occur depending on the dosage. *Investigations* Common (dose dependent): At high dosages the dilution effects may result in a corresponding dilution of blood components such as coagulation factors and other plasma proteins and in a decrease of hematocrit.

	Japan HES70 (Hespander fluid solution, Salinhes fluid solution 6%)	Japan HES130 (Voluven 6% solution for infusion)	EU (SmPC) HES130
		Other Precautions In an overseas clinical study, it has been reported that the use of HES preparations for fluid management during cardiac surgery using cardiopulmonary bypass in adults was associated with higher risks of postoperative bleeding requiring blood transfusion and reoperation due to bleeding, as compared with albumin.	
Burns	(No description)	(No description)	Contraindications - Burns
Dehydration	Contraindications Patients with dehydration or renal disorder accompanied by oliguria, etc. [Renal failure may occur.]	(No description)	Contraindications - Dehydration
Organ transplantation	(No description)	(No description)	Contraindications - Organ transplant patients
Patients with renal failure	Contraindications Patients with dehydration or renal disorder accompanied by oliguria, etc. [Renal failure may occur.]	Contraindications Patients with renal failure accompanied by oliguria or anuria [Excretion of this drug may be delayed in patients with renal failure.] Patients on dialysis [Excretion of this drug may be delayed.]	Contraindications - Renal impairment or renal replacement therapy

Appendix 3

Public literature

Appendix 3-1 Patients with sepsis

No.	Title	Author	Journal, etc.
1	Resuscitation fluid types in sepsis, surgical, and trauma patients: a systematic review and sequential network meta-analyses.	Tseng Chien-Hua, Chen Tzu-Tao, Wu Mei-Yi, Chan Ming-Cheng, Shih Ming-Chieh, Tu Yu-Kang	Critical care 2020; 24: 693.
2	Clinical characteristics and current interventions in shock patients in chinese emergency departments: a multicenter prospective cohort study.	Guo SB, Chen YX, Yu XZ	Chinese Medical Journal 2017; 130: 1146-54.
3	Fluid resuscitation practice patterns in intensive care units of the USA: a cross-sectional survey of critical care physicians.	Miller TE, Bunke M, Nisbet P, Brudney CS	Perioperative Medicine 2016; 5: 15.
4	The influence of hydroxyethyl starch on exogenous coagulation and active protein C in patients with septic shock.	Lyu Jie; Li Tong; Liu Fang; An Youzhong	Chinese Critical Care Medicine. 2015; 27: 28-32.

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No.	Title	Author	Journal, etc.
5	Acute kidney injury with hydroxyethyl starch 130/0.42 in severe sepsis.	Muller RB; Haase N; Lange T; Wetterslev J; Perner A	Acta Anaesthesiol Scandinavica 2015; 59: 329-36.
6	Long-term outcomes in patients with severe sepsis randomised to resuscitation with hydroxyethyl starch 130/0.42 or Ringer's acetate.	Perner Anders; Haase Nicolai; Winkel Per; Guttormsen Anne B; Tenhunen Jyrki; Klemenzson Gudmundur; Muller Rasmus G; Aneman Anders; Wetterslev Jorn	Intensive care medicine 2014; 40: 927-34.
7	Hydroxyethyl starch in sepsis.	Haase Nicolai, Rosenkrantz Segelcke	Danish Medical Jornal 2014; 61: B4764
8	Bleeding and risk of death with hydroxyethyl starch in severe sepsis: post hoc analyses of a randomized clinical trial.	Haase Nicolai; Wetterslev Jorn; Winkel Per; Perner Anders	Intensive care medicine 2013; 39: 2126-34.
9	Quality of life and pruritus in patients with severe sepsis resuscitated with hydroxyethyl starch long-term follow-up of a randomised trial.	Wittbrodt Piotr; Haase Nicolai; Butowska Dominika; Winding Robert; Poulsen Jesper B; Perner Anders	Critical care 2013; 17: R58.

Appendix 3-2 Critically ill patients

No.	Title	Author	Journal, etc.
1	Hydroxyethyl starch in sepsis.	Haase Nicolai Rosenkrantz Segelcke	Danish medical journal, 2014; 61: B4764.
2	Use of perioperative hydroxyethyl starch 6% and albumin 5% in elective joint arthroplasty and association with adverse outcomes: a retrospective population based analysis.	Opperer Mathias; Poeran Jashvant; Rasul Rehana; Mazumdar Madhu; Memtsoudis Stavros G	BMJ 2015; 350: h1567.
3	Hydroxyethyl starc and acute kidney injury in orthotopic liver transplantation: a single-center retrospective review.	Hand William R; Whiteley Joseph R; Epperson Tom I; Tam Lauren; Crego Heather; Wolf Bethany; Chavin Kenneth D; Taber David J	Anesthesia and analgesia 2015; 120: 619-626.
4	Acute kidney injury following severe trauma: risk factors and long-term outcome.	Eriksson Mikael; Brattstrom Olof; Martensson Johan; Larsson Emma; Oldner Anders	The journal of trauma and acute care surgery 2015; 79: 407-12.
5	Hydroxyethyl starch for fluid management in patients undergoing major abdominal surgery: a systematic review with meta-analysis and trial sequential analysis.	Pensier Joris; Deffontis Lucas; Rolle Amelie; Aarab Yassir; Capdevila Mathieu; Monet Clement; Carr Julie; Futier Emmanuel; Molinari Nicolas; Jaber Samir; Jong Audrey De	Anesthesia and analgesia 2022; 134: 686-95.

No.	Title	Author	Journal, etc.
6	Safety and efficacy of tetrastarches in surgery and trauma: a systematic review and meta-analysis of randomised controlled trials.	Chappell Daniel; van der Linden Philippe; Ripolles-Melchor Javier; James Michael F M	British journal of anaesthesia 2021; 127: 556-68.
7	Hydroxyethyl starch and acute kidney injury in high-risk patients undergoing cardiac surgery: a prospective multicenter study.	Nagore David; Candela Angel; Burge Martina; Monedero Pablo; Tamayo Eduardo; Alvarez J; Murie Manuel; Wijeysundera DN Duminda N; Vives Marc; On behalf of the Spanish perioperative cardiac surgery research group	Journal of clinical anesthesia 2021: 73; 110367.
8	Renal morbidity of 6% hydroxyethyl starch 130/0.4 in 9000 propensity score matched pairs of surgical patients.	Miyao H, Kotake Y	Anesthesia and analgesia 2020; 130: 1618-27.
9	Fluid resuscitation after severe trauma injury: u-shaped associations between tetrastarch dose and survival time or frequency of acute kidney failure.	Fleischhacker E; Trentzsch H; Kuppinger D; Piltz S; Beyer F; Meigel F; Kammerer T; Rehm M; Hartl W H	Medizinische Klinik, Intensivmedizin und Notfallmedizin, 2020; 115: 591-9.
10	The effects of perioperative intravenous fluid administration strategy on renal outcomes in patients undergoing cardiovascular surgery: an observational study.	Lee Eun-Ho; Yun Sung-Cheol; Lim Ye-Ji; Jo Jun-Young; Choi Dae-Kee; Choi In-Cheol	Medicine 2019; 98: e14383.

No.	Title	Author	Journal, etc.
11	Balanced 10% hydroxyethyl starch compared with balanced 6% hydroxyethyl starch and balanced crystalloid using a goal-directed hemodynamic algorithm in pancreatic surgery: a randomized clinical trial.	Werner Julia; Hunsicker Oliver; Schneider Anja; Stein Henryk; Heymann Christian von; Freitag Adrian; Feldheiser Aarne; Wernecke Klaus-Dieter; Spies Claudia	Medicine 2018; 97: e0579.
12	Hydroxyethyl starch for volume expansion after subarachnoid haemorrhage and renal function: results of a retrospective analysis.	Bercker Sven; Winkelmann Tanja; Busch Thilo; Laudi Sven	PloS one 2018; 13: e0192832.
13	Influence of 6% hydroxyethyl starch 130/0.4 versus crystalloid solution on structural renal damage markers after coronary artery bypass grafting: a post hoc subgroup analysis of a prospective trial.	Datzmann Thomas; Hoenicka Markus; Reinelt Helmut; Liebold Andreas; Gorki Hagen	Journal of cardiothoracic and vascular anesthesia 2018; 32: 205-211.
14	Acute kidney injury in critically burned patients resuscitated with a protocol that includes low doses of hydroxyethyl starch.	Sanchez-Sanchez M; Garcia-de-Lorenzo A;Cachafeiro L; Herrero E; Asensio M J; Agrifoglio A; Flores E; Estebanez B; Extremera P; Iglesias C; Martinez J.R	Annals of burns and fire disasters 2016; 29: 183-8.
15	Modern hydroxyethyl starch and acute kidney injury after cardiac surgery: a prospective multicentre cohort.	Vives M; Callejas R; Duque P; Echarri G; Wijeysundera D N; Hernandez A; Sabate A; Bes-Rastrollo M; Monedero P	British journal of anaesthesia 2016; 117: 4458-63.

No.	Title	Author	Journal, etc.
16	Use of hydroxyethyl starch in leukocytapheresis procedures does not increase renal toxicity.	Pagano Monica B; Harmon Charles; Cooling Laura; Connelly-Smith Laura; Mann Steven A; Pham Huy P; Marques Marisa B; Schlueter Annette J; Case Rosemary; King Karen E; Cataife Guido; Wu Yanyun; Wong Edward C C; Winters Jeffrey L	Transfusion 2016; 56: 2848-56.
17	Impact of perioperative administration of 6 % hydroxyethyl starch 130/0.4 on serum cystatin C-derived renal function after radical prostatectomy: a single-centre retrospective study.	Sudfeld Stefan; Leyh-Bannurah Sami R; Budaus Lars; Graefen Markus; Reese Philip C; von Breunig Franziska; Reuter Daniel A; Saugel Bernd	BMC anesthesiology 2016; 16: 69.
18	Effect of hydroxyethyl starch solution on incidence of acute kidney injury in patients suffering from cerebral vasospasm following aneurysmal subarachnoid hemorrhage.	Kieninger Martin; Unbekannt Daniel; Schneiker Andre; Sinner Barbara; Bele Sylvia; Prasser Christopher	Neurocritical care 2017; 26: 34-40.
19	Effect of hydroxyethyl starch on acute kidney injury after living donor hepatectomy.	Kim S-K; Choi S-S; Sim J-H; Baik J; Hwang S; Lee S-G; Kim Y-K	Transplantation proceedings 2016; 48: 102-6.

No.	Title	Author	Journal, etc.
20	Investigation regarding the correlation between hydroxyethyl starch administration and acute kidney injury in critically ill patients.	Wang Zhengguang; Zhang Mucheng; Wang Jianlei; Fang Xiangqun; Zheng Shaopeng; Zhang Quchu	Chin Crit Care Med. 2015; 27: 338-42.
21	The effect of 6% hydroxyethyl starch 130/0.4 on renal function, arterial blood pressure, and vasoactive hormones during radical prostatectomy: a randomized controlled trial.	Kancir Anne Sophie Pinholt; Johansen Joergen Kuhlwein; Ekeloef Niels Peter; Pedersen Erling Bjerregaard	Anesthesia and analgesia 2015; 120: 608-18.
22	Long-term outcomes in patients with severe sepsis randomised to resuscitation with hydroxyethyl starch 130/0.42 or Ringer's acetate.	Perner Anders; Haase Nicolai; Winkel Per; Guttormsen Anne B; Tenhunen Jyrki; Klemenzson Gudmundur; Muller Rasmus G; Aneman Anders; Wetterslev Jorn	Intensive care medicine 2014; 40: 927-34.
23	Early fluid resuscitation with hydroxyethyl starch 130/0.4 (6%) in severe burn injury: a randomized, controlled, double-blind clinical trial.	Bechir Markus; Puhan Milo A; Fasshauer Mario; Schuepbach Reto A; Stocker Reto; Neff Thomas A	Critical care 2013; 17: R299.

No.	Title	Author	Journal, etc.
24	Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial.	Annane Djillali; Siami Shidasp; Jaber Samir; Martin Claude; Elatrous Souheil; Declere Adrien Descorps; Preiser Jean Charles; Outin Herve; Troche Gilles; Charpentier Claire; Trouillet Jean Louis; Kimmoun Antoine; Forceville Xavier; Darmon Michael; Lesur Olivier; Reignier Jean; Regnier Jean; Abroug Fekri; Berger Philippe; Clec'h Christophe; Cle'h Christophe; Cousson Joel; Thibault Laure; Chevret Sylvie	JAMA 2013; 310: 1809-17.
25	Bleeding and risk of death with hydroxyethyl starch in severe sepsis: post hoc analyses of a randomized clinical trial.	Haase Nicolai; Wetterslev Jorn; Winkel Per; Perner Anders	Intensive care medicine 2013; 39: 2126-34.
26	Effects of different resuscitation fluid on severe acute pancreatitis.	Zhao Gang; Zhang Jun-Gang; Wu He-Shui; Tao Jin; Qin Qi; Deng Shi-Chang; Liu Yang; Liu Lin; Wang Bo; Tian Kui; Li Xiang; Zhu Shuai; Wang Chun-You	World journal of gastroenterology 2013; 19: 2044-52.

Appendix 3-3 Patients with severe hepatic impairment

No.	Title	Author	Journal, etc.
1	Plasma expanders for people with cirrhosis and large ascites treated with abdominal paracentesis.	Simonetti Rosa G; Perricone Giovanni; Nikolova Dimitrinka; Bjelakovic Goran; Gluud Christian	Cochrane database of systematic reviews 2019; 6: CD004039.
2	Comparing the effects of hydroxyethyl starch and albumin in cirrhotic patients with tense ascites; a randomized clinical trial.	Abootalebi Alireza; Khazaei Sepideh; Minakari Mohammad; Nasr-Isfahani Mohammad; Esmailian Mehrdad; Heydari Farhad	Advanced journal of emergency medicine 2017; 1: e7.

Appendix 3-4 Patients with thermal burn

No.	Title	Author	Journal, etc.
1	Acute kidney injury in critically burned patients resuscitated with a protocol that includes low doses of Hydroxyethyl Starch.	Sanchez-Sanchez M; Garcia-de-Lorenzo A; Cachafeiro L; Herrero E; Asensio M J; Agrifoglio A; Flores E; Estebanez B; Extremera P; Iglesias C; Martinez J R	Annals of burns and fire disasters 2016; 29: 183-188.
2	Early fluid resuscitation with hydroxyethyl starch 130/0.4 (6%) in severe burn injury: a randomized, controlled, double-blind clinical trial.	Bechir Markus; Puhan Milo A; Fasshauer Mario; Schuepbach Reto A; Stocker Reto; Neff Thomas A	Critical care 2013; 17: R299.

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Appendix 3-5 Organ transplant patients

No.	Title	Author	Journal, etc.
1	Effects of hydroxyethyl starch and gelatin on the risk of acute kidney injury following orthotopic liver transplantation: a multicenter retrospective comparative clinical study.	Chen Yingqi; Ning Xinyu; Lu Haiyang; Zhu Sainan; Wu Anshi; Jiang Jia; Mu Shanshan; Wang Jing; Niu Xu; Li Shengnan; Hou Lingdi; Zhao Yanxing; Lv Wenfei; Shang Meixia; Yao Chen; Han Shujun; Chi Ping; Xue Fushan; Yue Yun	Open medicine 2021; 16: 322-331
2	Early post-operative acute kidney injury after cardiac transplantation: incidence and predictive factors.	Jahangirifard Alireza; Ahmadi Zargham Hossein; Khalili Nastaran; Naghashzadeh Farah; Afshar Ali; Amiri Arvin; Dalili Nooshin	Clinical transplantation 2021; 35: e14420.
3	Effects of perioperative fluid replacement therapy in lung transplant patients.	Bjorkbom Emil; Hammainen Pekka; Schramko Alexey	Experimental and clinical transplantation 2017; 1: 78-81.
4	Hydroxyethyl starch and acute kidney injury in orthotopic liver transplantation: a single-center retrospective review.	Hand William R; Whiteley Joseph R; Epperson Tom I; Tam Lauren; Crego Heather; Wolf Bethany; Chavin Kenneth D; Taber David J	Anesthesia and analgesia, 2015; 120: 619-626.
5	Acute kidney injury within 72 hours after lung transplantation: incidence and perioperative risk factors.	Ishikawa Seiji; Griesdale Donald E G; Lohser Jens	Journal of cardiothoracic and vascular anesthesia 2014; 28: 931-5.

Appendix 4

Search conditions for public literature

Appendix 4-1 Patients with sepsis

Ichushi	#1 "Hydroxyethyl Starch Derivatives"/TH or "HES 130-0.4"/TH or ボルベン/al or VOLUVEN/al or サリンヘス/al or ヘスパンダー/al or Salinhes/al or Hespan/al or Hydroxyethylstarch/al or Hydroxyethyl-starch/al or "Hydroxyethyl starch"/al or ヒドロキシエチルスターチ/al or ヒドロキシエチル澱粉/al or "HES 130"/al or HES-130/al or HES130/al or "HES 70"/al or HES-70/al or HES70/al [939 件] #2 RD=ランダム化比較試験 or RD=準ランダム化比較試験 or ランダム化比較試験/TH or 準ランダム化比較試験/TH or ランダム割付け/TH or 一重盲検法/TH or 二重盲検法/TH or プラセボ/TH or ランダム/al or ランダマイ/al or 無作為/al or 盲検/al or ブラインド/al or シングルマスク/al or シングル・マスク/al or ダブルマスク/al or ダブル・マスク/al or トリプルマスク/al or トリプル・マスク/al or 実際的試験/al or 実際的研究/al or 実践的試験/al or 実践的研究/al or 実用的試験/al or 実用的研究/al or 実際的臨床試験/al or 実際的臨床研究/al or 実践的臨床試験/al or 実践的臨床研究/al or 実用的臨床試験/al or 実用的臨床研究/al or プラグマティック試験/al or プラグマティック研究/al or プラグマチック試験/al or プラグマチック研究/al or プラセボ/al or プラシーボ/al or 偽薬/al or 偽剤/al or RANDOM/al or BLIND/al or "SINGLE MASK"/al or SINGLE-MASK/al or "DOUBLE MASK"/al or DOUBLE-MASK/al or "TRIPLE MASK"/al or TRIPLE-MASK/al or "TREBLE MASK"/al or TREBLE-MASK/al or "pragmatic trial"/al or "pragmatic clinical trial"/al or "pragmatic stud"/al or "pragmatic clinical stud"/al or PLACEBO/al or RCT/al [100,693 件] #3 RD=比較研究 or 比較試験/AL or 比較臨床試験/AL or 比較薬理試験/AL or 比較研究/AL or 比較臨床研究/AL or 比較薬理研究/AL or クロスオーバー研究/TH or クロスオーバ/al or クロス・オーバ/AL or 交差試験/AL or 交差研究/AL or 交叉試験/AL or マッチドペア/al or 交叉研究/AL or COMPARAT/al or COMPARE/al or COMPARIS/al or "CROSS OVER"/AL or CROSSOVER/AL or CROSS-OVER/AL or "Matched Pair"/al or Matched-Pair/al [284,133 件]

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	#4 第 II 相試験/TH or 第 III 相試験/TH or 第 2 相/AL or 第 II 相/AL or 第二相/AL or フェーズ 2/AL or Phase2/AL or "Phase 2"/AL or フェーズ II/AL or "フェーズ II"/AL or PhaseII/AL or "Phase II"/AL or 第 3 相/AL or 第 III 相/AL or 第三相/AL or フェーズ 3/AL or Phase3/AL or "Phase 3"/AL or フェーズ III/AL or "フェーズ III"/AL or PhaseIII/AL or "Phase III"/AL or 用量設定試験/al or 用量反応試験/al or 薬量設定試験/al or 薬量反応試験/al or 投与量設定試験/al or 投与量反応試験/al [20,447 件] #5 介入試験/al or 介入研究/al or 介入調査/al or 介入的試験/al or 介入的研究/al or 介入的調査/al or "intervention stud"/al or "interventional stud"/al or "intervention trial"/al or "interventional trial"/al or intervention-stud/al or interventional-stud/al or intervention-trial/al or interventional-trial/al [5,992 件] #6 コホート研究/TH or 症例対照研究/TH or コホート/al or コーホート/al or コウホート/al or Cohort/al or 症例対照/al or 症例-対照/al or 症例・対照/al or 症例コントロール/al or 患者対照/al or 患者-対照/al or 患者・対照/al or 患者コントロール/al or ケースコントロール/al or ケース-コントロール/al or ケース・コントロール/al or ケースベース/al or ケース-ベース/al or ケース・ベース/al or ケースリファレン/al or ケース-リファレン/al or ケース・リファレン/al or ケースレファレン/al or ケース-レファレン/al or ケース・レファレン/al or "Case Control"/al or Case-Control/al or "Case Base"/al or Case-Base/al or "Case Compar"/al or Case-Compar/al or "Case Referen"/al or Case-Referen/al [31,382 件] #7 観察研究/TH or 観察研究/al or 観察試験/al or 観察調査/al or 観察的研究/al or 観察的試験/al or 観察的調査/al or 断面研究/al or 断面調査/al or 断面評価/al or 断面解析/al or 断面的研究/al or 断面的調査/al or 断面的評価/al or 断面的解析/al or 横断研究/al or 横断調査/al or 横断評価/al or 横断解析/al or 横断的研究/al or 横断的調査/al or 横断的評価/al or 横断的解析/al or クロスセクショナル研究/al or クロスセクショナル調査/al or クロスセクショナル評価/al or クロスセクショナル解析/al or クロス・セクショナル研究/al or クロス・セクショナル調査/al or クロス・セクショナル評価/al or クロス・セクショナル解析/al or 縦断研究/al or 縦断調査/al or 縦断評価/al or 縦断解析/al or 縦断的研究/al or 縦断的調査/al or 縦断的評価/al or 縦断的解析/al or 追跡研究/al or 追跡調査/al or 追跡評価/al or 追跡

	解析/al or 追跡的研究/al or 追跡的調査/al or 追跡的評価/al or 追跡的解析/al or 前向き/al or プロスペクティブ/al or 前方視/al or 後ろ向き/al or 後向き/al or レトロスペクティブ/al or 後方視/al or "Observational Study"/al or "cross-sectional Study"/al or "longitudinal study"/al or prospectiv/al or retrospectiv/al [215,395 件] #8 臨床試験/TH or 多施設共同研究/TH or 多施設/al or マルチセンタ/al or マルチ・センタ/al or 大規模臨床/al or バリデーション/al or メガトライアル/al or メガスタディ/al or 治験/al or 臨床試験/al or 臨床薬理試験/al or 評価試験/AL or 確認試験/al or 検証試験/al or 妥当性試験/al or 大規模試験/al or 臨床研究/al or 臨床薬理研究/al or 評価研究/AL or 確認研究/al or 検証研究/al or 妥当性研究/al or 大規模研究/al or Multicenter/al or Multi-center/al or Multicentre/al or Multi-centre/al or "clinical stud"/al or "Evaluation stud"/al or "Validation stud"/al or "mega stud"/al or "clinical trial"/al or "Evaluation trial"/al or "Validation trial"/al or "mega trial"/al [288,517 件] #9 製造販売後調査/TH or 市販後/AL or 市販直後/AL or 販売後/AL or 販売直後/AL or 製造販売後/AL or (製造販売後調査/TH or 特別調査/AL) or 使用成績/AL or 利用成績/AL or 医薬品再評価/al or "Post Market"/AL or Post-Market/AL or PostMarket/AL or EPPV/AL or フェーズ 4/AL or フェーズ-4/AL or フェーズ IV/AL or PHASE4/AL or PHASE-4/AL or "PHASE 4"/AL or PHASE-IV/AL or fourth-PHASE/AL or "PHASE IV"/AL or "fourth PHASE"/AL or 第 IV 相/AL or 第 4 相/AL or 第四相/AL or 臨床第 4/AL or 臨床第 IV/AL or 臨床第四/AL [13,652 件] #10 #1 and (#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9) [128 件] #11 (#10) and (PDAT=2013/6/1:2022/6/17 or IDAT=2013/6/1:2022/6/17) and (DT=2013:2022) [75 件] #12 ((#11 and (CK=ヒト or ヒト/TH or 人間/TH)) or (#11 not (CK=動物 or 動物/TH))) and (PT=原著論文,会議録,症例検討会) [51 件] #13 敗血症/TH or 敗血症/AL or 敗血病/AL or 敗血性疾患/AL or 菌血症/AL or セプシス/AL or Sepsis/AL or Septic/AL or Sapremia/AL or septicemia/AL or ゼプシス/AL or bacteremia/al [57,975 件] #14 #12 and #13 [1 件]

MEDLINE	L1 3497 SEA HYDROXYETHYL STARCH DERIVATIVES+NT/CT L2 4797 SEA VOLUVEN? OR HES130? OR HES70? OR (HYDROXYETHYL OR HYDROXY(W)ETHYL)(W)STARCH? OR HES(2A)(130? OR 70?) OR SALINHES? OR HESPAN# L3 1671969 SEA RANDOMIZED CONTROLLED TRIAL?/DT OR PRAGMATIC CLINICAL TRIAL/DT OR RANDOM ALLOCATION+NT/CT OR (SINGLE-BLIND METHOD+NT OR DOUBLE-BLIND METHOD+NT)/CT OR (SINGL? OR DOUBLE? OR TREBL? OR TRIPL?)(W)(BLIND? OR MASK?) OR RANDOM? OR PRAGMATIC?(3W)(STUD? OR TRIAL? OR TEST?) OR PLACEBO? OR RCT L4 3260039 SEA COMPARATIVE STUDY/DT OR CONTROLLED CLINICAL TRIAL?/DT OR (CROSS-OVER STUDIES+NT OR MATCHED-PAIR ANALYSIS+NT)/CT OR (COMPARATIVE? OR COMPARE? OR COMPARIS? OR CONTROLLED OR CROSS(1W)OVER? OR CROSSOVER? OR MATCH?(W)PAIR)(3A)(STUD? OR TRIAL? OR TEST? OR DRUG? OR EVALUAT? OR ANALYS?) L5 242122 SEA (CLINICAL TRIAL, PHASE II OR CLINICAL TRIAL, PHASE III OR CLINICAL TRIAL, PHASE IV)/DT OR PHASE(1A)(1 OR I OR 1ST OR FIRST OR 2 OR II OR 2ND OR SECOND OR 3 OR III OR 3RD OR THIRD OR 4 OR IV OR FOURTH OR 4TH) L6 13341 SEA PHASE1 OR PHASEI OR PHASE2 OR PHASEII OR PHASE3 OR PHASEIII OR PHASE4 OR PHASEIV OR POSTMARKET? OR POST(1W)MARKET? L7 107504 SEA INTERVENTION?(3A)(STUD? OR TRIAL? OR TEST?) L8 2962998 SEA (COHORT STUDIES+NT OR CASE-CONTROL STUDIES+NT)/CT OR COHORT? OR CASE(1W)(CONTROL? OR BASE? OR COMPAR? OR REFER?) L9 2841736 SEA OBSERVATIONAL STUDY?/DT OR CROSS-SECTIONAL STUDIES+NT/CT OR (OBSERV? OR

	NON(1W)EXPERIMENT? OR NONEXPERIMENT? OR CROSS(1W)SECTION? OR CROSSSECTION? OR LONGITUDINAL? OR PROSPECTIVE? OR RETROSPECTIVE?)(3A)(STUD? OR TRIAL? OR TEST? OR SURVEY? OR DESIGN? OR RESEARCH? OR EVALUAT? OR ANALYS?) L10 1486916 SEA (CLINICAL STUDY OR CLINICAL TRIAL? OR EVALUATION STUDY OR MULTICENTER STUDY OR VALIDATION STUDY)/DT L11 2417283 SEA (CLINICAL? OR EVALUAT? OR MULTICENT? OR MULTI(W)CENT? OR LARGE(W)SCALE OR VALIDATION?)(3A)(STUD? OR TRIAL? OR TEST? OR SURVEY? OR DESIGN? OR RESEARCH? OR EVALUAT? OR ANALYS?) OR MEGA(W)(STUD? OR TRIAL?) OR MEGASTUD? OR MEGATRIAL? L12 696 SEA (L1 OR L2) AND (L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10) AND (20130601-20220617/ED OR 20130601-20220617/UP) AND 2013-2022/PY L13 437 SEA (L12/HUMAN OR (L12 NOT ANIMALS/CT)) NOT REVIEW/DT AND ARTICLE/DT L14 136137 SEA SEPSIS+NT/CT L15 230358 SEA SEPSIS? OR SEPTIC? OR SAPREMIA? OR SEPTICEMIA? OR BACTEREMIA? OR BACTERAEMIA? OR BACILLAEMIA? OR BACILLEMIA? L16 2339 SEA SEPSIS+NT/CT(L)CI/CT L17 249194 SEA (L14 OR L15) NOT L16 L18 60 SEA L13 AND L17 D L18 ALL 1-60

Appendix 4-2 Critically ill patients

Ichushi	#1 "Hydroxyethyl Starch Derivatives"/TH or "HES 130-0.4"/TH or ボルベン/al or VOLUVEN/al or サリンヘス/al or ヘスパンダー/al or Salinhes/al or Hespan/al or Hydroxyethylstarch/al or Hydroxyethyl-starch/al or "Hydroxyethyl starch"/al or ヒドロキシエチルスターチ/al or ヒドロキシエチル澱粉/al or "HES 130"/al or HES-130/al or HES130/al or "HES 70"/al or HES-70/al or HES70/al [939 件] #2 RD=ランダム化比較試験 or RD=準ランダム化比較試験 or ランダム化比較試験/TH or 準ランダム化比較試験/TH or ランダム割付け/TH or 一重盲検法/TH or 二重盲検法/TH or プラセボ/TH or ランダム/al or ランダマイ/al or 無作為/al or 盲検/al or ブラインド/al or シングルマスク/al or シングル・マスク/al or ダブルマスク/al or ダブル・マスク/al or トリプルマスク/al or トリプル・マスク/al or 実際的試験/al or 実際的研究/al or 実践的試験/al or 実践的研究/al or 実用的試験/al or 実用的研究/al or 実際的臨床試験/al or 実際的臨床研究/al or 実践的臨床試験/al or 実践的臨床研究/al or 実用的臨床試験/al or 実用的臨床研究/al or プラグマティック試験/al or プラグマティック研究/al or プラグマチック試験/al or プラグマチック研究/al or プラセボ/al or プラシーボ/al or 偽薬/al or 偽剤/al or RANDOM/al or BLIND/al or "SINGLE MASK"/al or SINGLE-MASK/al or "DOUBLE MASK"/al or DOUBLE-MASK/al or "TRIPLE MASK"/al or TRIPLE-MASK/al or "TREBLE MASK"/al or TREBLE-MASK/al or "pragmatic trial"/al or "pragmatic clinical trial"/al or "pragmatic stud"/al or "pragmatic clinical stud"/al or PLACEBO/al or RCT/al [100,693 件] #3 RD=比較研究 or 比較試験/AL or 比較臨床試験/AL or 比較薬理試験/AL or 比較研究/AL or 比較臨床研究/AL or 比較薬理研究/AL or クロスオーバー研究/TH or クロスオーバ/al or クロス・オーバ/AL or 交差試験/AL or 交差研究/AL or 交叉試験/AL or マッチドペア/al or 交叉研究/AL or COMPARAT/al or COMPARE/al or COMPARIS/al or "CROSS OVER"/AL or CROSSOVER/AL or CROSS-OVER/AL or "Matched Pair"/al or Matched-Pair/al [284,133 件] #4 第 II 相試験/TH or 第 III 相試験/TH or 第 2 相/AL or 第 II 相/AL or 第二相/AL or フェーズ 2/AL or Phase2/AL or "Phase 2"/AL or フェーズ II/AL or "フェーズ II"/AL or PhaseII/AL or "Phase II"/AL or 第 3 相/AL or 第 III 相/AL or 第三相/AL or フェーズ 3/AL or Phase3/AL

	or "Phase 3"/AL or フェーズ III/AL or "フェーズ III"/AL or PhaseIII/AL or "Phase III"/AL or 用量設定試験/al or 用量反応試験/al or 薬量設定試験/al or 薬量反応試験/al or 投与量設定試験/al or 投与量反応試験/al [20,447 件] #5 介入試験/al or 介入研究/al or 介入調査/al or 介入的試験/al or 介入的研究/al or 介入的調査/al or "intervention stud"/al or "interventional stud"/al or "intervention trial"/al or "interventional trial"/al or intervention-stud/al or interventional-stud/al or intervention-trial/al or interventional-trial/al [5,992 件] #6 コホート研究/TH or 症例対照研究/TH or コホート/al or コーホート/al or コウホート/al or Cohort/al or 症例対照/al or 症例-対照/al or 症例・対照/al or 症例コントロール/al or 患者対照/al or 患者-対照/al or 患者・対照/al or 患者コントロール/al or ケースコントロール/al or ケース-コントロール/al or ケース・コントロール/al or ケースベース/al or ケース-ベース/al or ケース・ベース/al or ケースリファレン/al or ケース-リファレン/al or ケース・リファレン/al or ケースレファレン/al or ケース-レファレン/al or ケース・レファレン/al or "Case Control"/al or Case-Control/al or "Case Base"/al or Case-Base/al or "Case Compar"/al or Case-Compar/al or "Case Referen"/al or Case-Referen/al [31,382 件] #7 観察研究/TH or 観察研究/al or 観察試験/al or 観察調査/al or 観察的研究/al or 観察的試験/al or 観察的調査/al or 断面研究/al or 断面調査/al or 断面評価/al or 断面解析/al or 断面的研究/al or 断面的調査/al or 断面的評価/al or 断面的解析/al or 横断研究/al or 横断調査/al or 横断評価/al or 横断解析/al or 横断的研究/al or 横断的調査/al or 横断的評価/al or 横断的解析/al or クロスセクショナル研究/al or クロスセクショナル調査/al or クロスセクショナル評価/al or クロスセクショナル解析/al or クロス・セクショナル研究/al or クロス・セクショナル調査/al or クロス・セクショナル評価/al or クロス・セクショナル解析/al or 縦断研究/al or 縦断調査/al or 縦断評価/al or 縦断解析/al or 縦断的研究/al or 縦断的調査/al or 縦断的評価/al or 縦断的解析/al or 追跡研究/al or 追跡調査/al or 追跡評価/al or 追跡解析/al or 追跡的研究/al or 追跡的調査/al or 追跡的評価/al or 追跡的解析/al or 前向き/al or プロスペクティブ/al or 前方視/al or 後ろ向き/al or 後向き/al or レトロスペクティブ/al or 後方視/al or "Observational Study"/al or "cross-sectional Study"/al or "longitudinal

	study"/al or prospectiv/al or retrospectiv/al [215,395 件] #8 臨床試験/TH or 多施設共同研究/TH or 多施設/al or マルチセンタ/al or マルチ・センタ/al or 大規模臨床/al or バリデーション/al or メガトライアル/al or メガスタディ/al or 治験/al or 臨床試験/al or 臨床薬理試験/al or 評価試験/AL or 確認試験/al or 検証試験/al or 妥当性試験/al or 大規模試験/al or 臨床研究/al or 臨床薬理研究/al or 評価研究/AL or 確認研究/al or 検証研究/al or 妥当性研究/al or 大規模研究/al or Multicenter/al or Multi-center/al or Multicentre/al or Multi-centre/al or "clinical stud"/al or "Evaluation stud"/al or "Validation stud"/al or "mega stud"/al or "clinical trial"/al or "Evaluation trial"/al or "Validation trial"/al or "mega trial"/al [288,517 件] #9 製造販売後調査/TH or 市販後/AL or 市販直後/AL or 販売後/AL or 販売直後/AL or 製造販売後/AL or (製造販売後調査/TH or 特別調査/AL) or 使用成績/AL or 利用成績/AL or 医薬品再評価/al or "Post Market"/AL or Post-Market/AL or PostMarket/AL or EPPV/AL or フェーズ 4/AL or フェーズ-4/AL or フェーズ IV/AL or PHASE4/AL or PHASE-4/AL or "PHASE 4"/AL or PHASE-IV/AL or fourth-PHASE/AL or "PHASE IV"/AL or "fourth PHASE"/AL or 第 IV 相/AL or 第 4 相/AL or 第四相/AL or 臨床第 4/AL or 臨床第 IV/AL or 臨床第四/AL [13,652 件] #10 #1 and (#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9) [128 件] #11 (#10) and (PDAT=2013/6/1:2022/6/17 or IDAT=2013/6/1:2022/6/17) and (DT=2013:2022) [75 件] #12 ((#11 and (CK=ヒト or ヒト/TH or 人間/TH)) or (#11 not (CK=動物 or 動物/TH))) and (PT=原著論文,会議録,症例検討会) [51 件] #13 (重症/al not 重症度/al) or 重度/al or 重篤/al or severe/al or life-threaten/al or "life threaten"/al or "critically ill"/al or critically-ill/al [221,973 件] #14 #12 and #13 [1 件]

MEDLINE	L1 3497 SEA HYDROXYETHYL STARCH DERIVATIVES+NT/CT L2 4797 SEA VOLUVEN? OR HES130? OR HES70? OR (HYDROXYETHYL OR HYDROXY(W)ETHYL)(W)STARCH? OR HES(2A)(130? OR 70?) OR SALINHES? OR HESPAN# L3 1671969 SEA RANDOMIZED CONTROLLED TRIAL?/DT OR PRAGMATIC CLINICAL TRIAL/DT OR RANDOM ALLOCATION+NT/CT OR (SINGLE-BLIND METHOD+NT OR DOUBLE-BLIND METHOD+NT)/CT OR (SINGL? OR DOUBLE? OR TREBL? OR TRIPL?)(W)(BLIND? OR MASK?) OR RANDOM? OR PRAGMATIC?(3W)(STUD? OR TRIAL? OR TEST?) OR PLACEBO? OR RCT L4 3260039 SEA COMPARATIVE STUDY/DT OR CONTROLLED CLINICAL TRIAL?/DT OR (CROSS-OVER STUDIES+NT OR MATCHED-PAIR ANALYSIS+NT)/CT OR (COMPARATIVE? OR COMPARE? OR COMPARIS? OR CONTROLLED OR CROSS(1W)OVER? OR CROSSOVER? OR MATCH?(W)PAIR)(3A)(STUD? OR TRIAL? OR TEST? OR DRUG? OR EVALUAT? OR ANALYS?) L5 242122 SEA (CLINICAL TRIAL, PHASE II OR CLINICAL TRIAL, PHASE III OR CLINICAL TRIAL, PHASE IV)/DT OR PHASE(1A)(1 OR I OR 1ST OR FIRST OR 2 OR II OR 2ND OR SECOND OR 3 OR III OR 3RD OR THIRD OR 4 OR IV OR FOURTH OR 4TH) L6 13341 SEA PHASE1 OR PHASEI OR PHASE2 OR PHASEII OR PHASE3 OR PHASEIII OR PHASE4 OR PHASEIV OR POSTMARKET? OR POST(1W)MARKET? L7 107504 SEA INTERVENTION?(3A)(STUD? OR TRIAL? OR TEST?) L8 2962998 SEA (COHORT STUDIES+NT OR CASE-CONTROL STUDIES+NT)/CT OR COHORT? OR CASE(1W)(CONTROL? OR BASE? OR COMPAR? OR REFER?) L9 2841736 SEA OBSERVATIONAL STUDY?/DT OR CROSS-SECTIONAL STUDIES+NT/CT OR (OBSERV? OR

	NON(1W)EXPERIMENT? OR NONEXPERIMENT? OR CROSS(1W)SECTION? OR CROSSSECTION? OR LONGITUDINAL? OR PROSPECTIVE? OR RETROSPECTIVE?)(3A)(STUD? OR TRIAL? OR TEST? OR SURVEY? OR DESIGN? OR RESEARCH? OR EVALUAT? OR ANALYS?) L10 1486916 SEA (CLINICAL STUDY OR CLINICAL TRIAL? OR EVALUATION STUDY OR MULTICENTER STUDY OR VALIDATION STUDY)/DT L11 2417283 SEA (CLINICAL? OR EVALUAT? OR MULTICENT? OR MULTI(W)CENT? OR LARGE(W)SCALE OR VALIDATION?)(3A)(STUD? OR TRIAL? OR TEST? OR SURVEY? OR DESIGN? OR RESEARCH? OR EVALUAT? OR ANALYS?) OR MEGA(W)(STUD? OR TRIAL?) OR MEGASTUD? OR MEGATRIAL? L12 696 SEA (L1 OR L2) AND (L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10) AND (20130601-20220617/ED OR 20130601-20220617/UP) AND 2013-2022/PY L13 437 SEA (L12/HUMAN OR (L12 NOT ANIMALS/CT)) NOT REVIEW/DT AND ARTICLE/DT L14 1342128 SEA SEVERE? OR LIFE(W)THREATEN? OR CRITICAL?(W)ILL L15 107 SEA L13 AND L14 L16 79 SEA L15 AND (L1/MAJ OR L2/TI OR L14/TI) D L16 ALL 1-79

Appendix 4-3 Patients with severe hepatic impairment

Ichushi	#1 "Hydroxyethyl Starch Derivatives"/TH or "HES 130-0.4"/TH or ボルベン/al or VOLUVEN/al or サリンヘス/al or ヘスパンダー/al or Salinhes/al or Hespan/al or Hydroxyethylstarch/al or Hydroxyethyl-starch/al or "Hydroxyethyl starch"/al or ヒドロキシエチルスターチ/al or ヒドロキシエチル澱粉/al or "HES 130"/al or HES-130/al or HES130/al or "HES 70"/al or HES-70/al or HES70/al [939 件] #2 RD=ランダム化比較試験 or RD=準ランダム化比較試験 or ランダム化比較試験/TH or 準ランダム化比較試験/TH or ランダム割付け/TH or 一重盲検法/TH or 二重盲検法/TH or プラセボ/TH or ランダム/al or ランダマイ/al or 無作為/al or 盲検/al or ブラインド/al or シングルマスク/al or シングル・マスク/al or ダブルマスク/al or ダブル・マスク/al or トリプルマスク/al or トリプル・マスク/al or 実際的試験/al or 実際的研究/al or 実践的試験/al or 実践的研究/al or 実用的試験/al or 実用的研究/al or 実際的臨床試験/al or 実際的臨床研究/al or 実践的臨床試験/al or 実践的臨床研究/al or 実用的臨床試験/al or 実用的臨床研究/al or プラグマティック試験/al or プラグマティック研究/al or プラグマチック試験/al or プラグマチック研究/al or プラセボ/al or プラシーボ/al or 偽薬/al or 偽剤/al or RANDOM/al or BLIND/al or "SINGLE MASK"/al or SINGLE-MASK/al or "DOUBLE MASK"/al or DOUBLE-MASK/al or "TRIPLE MASK"/al or TRIPLE-MASK/al or "TREBLE MASK"/al or TREBLE-MASK/al or "pragmatic trial"/al or "pragmatic clinical trial"/al or "pragmatic stud"/al or "pragmatic clinical stud"/al or PLACEBO/al or RCT/al [100,693 件] #3 RD=比較研究 or 比較試験/AL or 比較臨床試験/AL or 比較薬理試験/AL or 比較研究/AL or 比較臨床研究/AL or 比較薬理研究/AL or クロスオーバー研究/TH or クロスオーバ/al or クロス・オーバ/AL or 交差試験/AL or 交差研究/AL or 交叉試験/AL or マッチドペア/al or 交叉研究/AL or COMPARAT/al or COMPARE/al or COMPARIS/al or "CROSS OVER"/AL or CROSSOVER/AL or CROSS-OVER/AL or "Matched Pair"/al or Matched-Pair/al [284,133 件] #4 第 II 相試験/TH or 第 III 相試験/TH or 第 2 相/AL or 第 II 相/AL or 第二相/AL or フェーズ 2/AL or Phase2/AL or "Phase 2"/AL or フェーズ II/AL or "フェーズ II"/AL or PhaseII/AL or "Phase II"/AL or 第 3 相/AL or 第 III 相/AL or 第三相/AL or フェーズ 3/AL or Phase3/AL

	or "Phase 3"/AL or フェーズ III/AL or "フェーズ III"/AL or PhaseIII/AL or "Phase III"/AL or 用量設定試験/al or 用量反応試験/al or 薬量設定試験/al or 薬量反応試験/al or 投与量設定試験/al or 投与量反応試験/al [20,447 件] #5 介入試験/al or 介入研究/al or 介入調査/al or 介入的試験/al or 介入的研究/al or 介入的調査/al or "intervention stud"/al or "interventional stud"/al or "intervention trial"/al or "interventional trial"/al or intervention-stud/al or interventional-stud/al or intervention-trial/al or interventional-trial/al [5,992 件] #6 コホート研究/TH or 症例対照研究/TH or コホート/al or コーホート/al or コウホート/al or Cohort/al or 症例対照/al or 症例-対照/al or 症例・対照/al or 症例コントロール/al or 患者対照/al or 患者-対照/al or 患者・対照/al or 患者コントロール/al or ケースコントロール/al or ケース-コントロール/al or ケース・コントロール/al or ケースベース/al or ケース-ベース/al or ケース・ベース/al or ケースリファレン/al or ケース-リファレン/al or ケース・リファレン/al or ケースレファレン/al or ケース-レファレン/al or ケース・レファレン/al or "Case Control"/al or Case-Control/al or "Case Base"/al or Case-Base/al or "Case Compar"/al or Case-Compar/al or "Case Referen"/al or Case-Referen/al [31,382 件] #7 観察研究/TH or 観察研究/al or 観察試験/al or 観察調査/al or 観察的研究/al or 観察的試験/al or 観察的調査/al or 断面研究/al or 断面調査/al or 断面評価/al or 断面解析/al or 断面的研究/al or 断面的調査/al or 断面的評価/al or 断面的解析/al or 横断研究/al or 横断調査/al or 横断評価/al or 横断解析/al or 横断的研究/al or 横断的調査/al or 横断的評価/al or 横断的解析/al or クロスセクショナル研究/al or クロスセクショナル調査/al or クロスセクショナル評価/al or クロスセクショナル解析/al or クロス・セクショナル研究/al or クロス・セクショナル調査/al or クロス・セクショナル評価/al or クロス・セクショナル解析/al or 縦断研究/al or 縦断調査/al or 縦断評価/al or 縦断解析/al or 縦断的研究/al or 縦断的調査/al or 縦断的評価/al or 縦断的解析/al or 追跡研究/al or 追跡調査/al or 追跡評価/al or 追跡解析/al or 追跡的研究/al or 追跡的調査/al or 追跡的評価/al or 追跡的解析/al or 前向き/al or プロスペクティブ/al or 前方視/al or 後ろ向き/al or 後向き/al or レトロスペクティブ/al or 後方視/al or "Observational Study"/al or "cross-sectional Study"/al or "longitudinal

	study"/al or prospectiv/al or retrospectiv/al [215,395 件] #8 臨床試験/TH or 多施設共同研究/TH or 多施設/al or マルチセンタ/al or マルチ・センタ/al or 大規模臨床/al or バリデーション/al or メガトライアル/al or メガスタディ/al or 治験/al or 臨床試験/al or 臨床薬理試験/al or 評価試験/AL or 確認試験/al or 検証試験/al or 妥当性試験/al or 大規模試験/al or 臨床研究/al or 臨床薬理研究/al or 評価研究/AL or 確認研究/al or 検証研究/al or 妥当性研究/al or 大規模研究/al or Multicenter/al or Multi-center/al or Multicentre/al or Multi-centre/al or "clinical stud"/al or "Evaluation stud"/al or "Validation stud"/al or "mega stud"/al or "clinical trial"/al or "Evaluation trial"/al or "Validation trial"/al or "mega trial"/al [288,517 件] #9 製造販売後調査/TH or 市販後/AL or 市販直後/AL or 販売後/AL or 販売直後/AL or 製造販売後/AL or (製造販売後調査/TH or 特別調査/AL) or 使用成績/AL or 利用成績/AL or 医薬品再評価/al or "Post Market"/AL or Post-Market/AL or PostMarket/AL or EPPV/AL or フェーズ 4/AL or フェーズ-4/AL or フェーズ IV/AL or PHASE4/AL or PHASE-4/AL or "PHASE 4"/AL or PHASE-IV/AL or fourth-PHASE/AL or "PHASE IV"/AL or "fourth PHASE"/AL or 第 IV 相/AL or 第 4 相/AL or 第四相/AL or 臨床第 4/AL or 臨床第 IV/AL or 臨床第四/AL [13,652 件] #10 #1 and (#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9) [128 件] #11 (#10) and (PDAT=2013/6/1:2022/6/17 or IDAT=2013/6/1:2022/6/17) and (DT=2013:2022) [75 件] #12 ((#11 and (CK=ヒト or ヒト/TH or 人間/TH)) or (#11 not (CK=動物 or 動物/TH))) and (PT=原著論文,会議録,症例検討会) [51 件] #13 肝臓疾患/TH or 肝疾患/AL or 肝障害/AL or 肝機能障害/AL or 肝腫瘤性疾患/AL or 肝臓疾患/AL or 肝臓病/AL or 肝病変/AL or 肝分葉異常/AL or 肝葉萎縮/AL or 障害肝/AL or 肝右葉低形成/AL or 肝機能低下/AL or 肝臓機能低下/AL or 肝臓機能障害/AL or 肝臓障害/AL or 肝機能異常/AL or 肝傷害/AL or 肝臓傷害/AL or 肝機能傷害/AL or 肝臓機能傷害/AL or "liver DISEASE"/al or "liver Disorder"/al or "liver failure"/al or "liver dysfunction"/al or "liver insufficien"/al [432,682 件]

	#14 #12 and #13 [2 件]
MEDLINE	L1 3497 SEA HYDROXYETHYL STARCH DERIVATIVES+NT/CT L2 4797 SEA VOLUVEN? OR HES130? OR HES70? OR (HYDROXYETHYL OR HYDROXY(W)ETHYL)(W)STARCH? OR HES(2A)(130? OR 70?) OR SALINHES? OR HESPAN# L3 1671969 SEA RANDOMIZED CONTROLLED TRIAL?/DT OR PRAGMATIC CLINICAL TRIAL/DT OR RANDOM ALLOCATION+NT/CT OR (SINGLE-BLIND METHOD+NT OR DOUBLE-BLIND METHOD+NT)/CT OR (SINGL? OR DOUBLE? OR TREBL? OR TRIPL?)(W)(BLIND? OR MASK?) OR RANDOM? OR PRAGMATIC?(3W)(STUD? OR TRIAL? OR TEST?) OR PLACEBO? OR RCT L4 3260039 SEA COMPARATIVE STUDY/DT OR CONTROLLED CLINICAL TRIAL?/DT OR (CROSS-OVER STUDIES+NT OR MATCHED-PAIR ANALYSIS+NT)/CT OR (COMPARATIVE? OR COMPARE? OR COMPARIS? OR CONTROLLED OR CROSS(1W)OVER? OR CROSSOVER? OR MATCH?(W)PAIR)(3A)(STUD? OR TRIAL? OR TEST? OR DRUG? OR EVALUAT? OR ANALYS?) L5 242122 SEA (CLINICAL TRIAL, PHASE II OR CLINICAL TRIAL, PHASE III OR CLINICAL TRIAL, PHASE IV)/DT OR PHASE(1A)(1 OR I OR 1ST OR FIRST OR 2 OR II OR 2ND OR SECOND OR 3 OR III OR 3RD OR THIRD OR 4 OR IV OR FOURTH OR 4TH) L6 13341 SEA PHASE1 OR PHASEI OR PHASE2 OR PHASEII OR PHASE3 OR PHASEIII OR PHASE4 OR PHASEIV OR POSTMARKET? OR POST(1W)MARKET? L7 107504 SEA INTERVENTION?(3A)(STUD? OR TRIAL? OR TEST?) L8 2962998 SEA (COHORT STUDIES+NT OR CASE-CONTROL STUDIES+NT)/CT OR COHORT? OR CASE(1W)(CONTROL? OR

	BASE? OR COMPAR? OR REFER?) L9 2841736 SEA OBSERVATIONAL STUDY?/DT OR CROSS-SECTIONAL STUDIES+NT/CT OR (OBSERV? OR NON(1W)EXPERIMENT? OR NONEXPERIMENT? OR CROSS(1W)SECTION? OR CROSSSECTION? OR LONGITUDINAL? OR PROSPECTIVE? OR RETROSPECTIVE?)(3A)(STUD? OR TRIAL? OR TEST? OR SURVEY? OR DESIGN? OR RESEARCH? OR EVALUAT? OR ANALYS?) L10 1486916 SEA (CLINICAL STUDY OR CLINICAL TRIAL? OR EVALUATION STUDY OR MULTICENTER STUDY OR VALIDATION STUDY)/DT L11 2417283 SEA (CLINICAL? OR EVALUAT? OR MULTICENT? OR MULTI(W)CENT? OR LARGE(W)SCALE OR VALIDATION?)(3A)(STUD? OR TRIAL? OR TEST? OR SURVEY? OR DESIGN? OR RESEARCH? OR EVALUAT? OR ANALYS?) OR MEGA(W)(STUD? OR TRIAL?) OR MEGASTUD? OR MEGATRIAL? L12 696 SEA (L1 OR L2) AND (L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10) AND (20130601-20220617/ED OR 20130601-20220617/UP) AND 2013-2022/PY L13 437 SEA (L12/HUMAN OR (L12 NOT ANIMALS/CT)) NOT REVIEW/DT AND ARTICLE/DT L14 604426 SEA LIVER DISEASES+NT/CT L15 344931 SEA (LIVER OR HEPAT?)(2A)(FAILUR? OR INSUFFICIEN? OR DISEASE? OR DYSFUNCT? OR FUNCT? OR ABNORMAL? OR DISORDER OR INJ?) L16 23 SEA L13 AND (L14 OR L15) L17 20475 SEA LIVER DISEASES+NT/CT(L)CI/CT L18 23 SEA L16 NOT L17

	D L18 ALL 1-23

Appendix 4-4 Patients with severe coagulation disorder

Ichushi	#1 "Hydroxyethyl Starch Derivatives"/TH or "HES 130-0.4"/TH or ボルベン/al or VOLUVEN/al or サリンヘス/al or ヘスパンダー/al or Salinhes/al or Hespan/al or Hydroxyethylstarch/al or Hydroxyethyl-starch/al or "Hydroxyethyl starch"/al or ヒドロキシエチルスターチ/al or ヒドロキシエチル澱粉/al or "HES 130"/al or HES-130/al or HES130/al or "HES 70"/al or HES-70/al or HES70/al [939 件] #2 RD=ランダム化比較試験 or RD=準ランダム化比較試験 or ランダム化比較試験/TH or 準ランダム化比較試験/TH or ランダム割付け/TH or 一重盲検法/TH or 二重盲検法/TH or プラセボ/TH or ランダム/al or ランダマイ/al or 無作為/al or 盲検/al or ブラインド/al or シングルマスク/al or シングル・マスク/al or ダブルマスク/al or ダブル・マスク/al or トリプルマスク/al or トリプル・マスク/al or 実際的試験/al or 実際的研究/al or 実践的試験/al or 実践的研究/al or 実用的試験/al or 実用的研究/al or 実際的臨床試験/al or 実際的臨床研究/al or 実践的臨床試験/al or 実践的臨床研究/al or 実用的臨床試験/al or 実用的臨床研究/al or プラグマティック試験/al or プラグマティック研究/al or プラグマチック試験/al or プラグマチック研究/al or プラセボ/al or プラシーボ/al or 偽薬/al or 偽剤/al or RANDOM/al or BLIND/al or "SINGLE MASK"/al or SINGLE-MASK/al or "DOUBLE MASK"/al or DOUBLE-MASK/al or "TRIPLE MASK"/al or TRIPLE-MASK/al or "TREBLE MASK"/al or TREBLE-MASK/al or "pragmatic trial"/al or "pragmatic clinical trial"/al or "pragmatic stud"/al or "pragmatic clinical stud"/al or PLACEBO/al or RCT/al [100,693 件] #3 RD=比較研究 or 比較試験/AL or 比較臨床試験/AL or 比較薬理試験/AL or 比較研究/AL or 比較臨床研究/AL or 比較薬理研究/AL or クロスオーバー研究/TH or クロスオーバ/al or クロス・オーバ/AL or 交差試験/AL or 交差研究/AL or 交叉試験/AL or マッチドペア/al or 交叉研究/AL or COMPARAT/al or COMPARE/al or COMPARIS/al or "CROSS OVER"/AL or CROSSOVER/AL or CROSS-OVER/AL or "Matched Pair"/al or Matched-Pair/al [284,133 件] #4 第 II 相試験/TH or 第 III 相試験/TH or 第 2 相/AL or 第 II 相/AL or 第二相/AL or フェーズ 2/AL or Phase2/AL or "Phase 2"/AL or フェーズ II/AL or "フェーズ II"/AL or PhaseII/AL or "Phase II"/AL or 第 3 相/AL or 第 III 相/AL or 第三相/AL or フェーズ 3/AL or Phase3/AL

	or "Phase 3"/AL or フェーズ III/AL or "フェーズ III"/AL or PhaseIII/AL or "Phase III"/AL or 用量設定試験/al or 用量反応試験/al or 薬量設定試験/al or 薬量反応試験/al or 投与量設定試験/al or 投与量反応試験/al [20,447 件] #5 介入試験/al or 介入研究/al or 介入調査/al or 介入的試験/al or 介入的研究/al or 介入的調査/al or "intervention stud"/al or "interventional stud"/al or "intervention trial"/al or "interventional trial"/al or intervention-stud/al or interventional-stud/al or intervention-trial/al or interventional-trial/al [5,992 件] #6 コホート研究/TH or 症例対照研究/TH or コホート/al or コーホート/al or コウホート/al or Cohort/al or 症例対照/al or 症例-対照/al or 症例・対照/al or 症例コントロール/al or 患者対照/al or 患者-対照/al or 患者・対照/al or 患者コントロール/al or ケースコントロール/al or ケース-コントロール/al or ケース・コントロール/al or ケースベース/al or ケース-ベース/al or ケース・ベース/al or ケースリファレン/al or ケース-リファレン/al or ケース・リファレン/al or ケースレファレン/al or ケース-レファレン/al or ケース・レファレン/al or "Case Control"/al or Case-Control/al or "Case Base"/al or Case-Base/al or "Case Compar"/al or Case-Compar/al or "Case Referen"/al or Case-Referen/al [31,382 件] #7 観察研究/TH or 観察研究/al or 観察試験/al or 観察調査/al or 観察的研究/al or 観察的試験/al or 観察的調査/al or 断面研究/al or 断面調査/al or 断面評価/al or 断面解析/al or 断面的研究/al or 断面的調査/al or 断面的評価/al or 断面的解析/al or 横断研究/al or 横断調査/al or 横断評価/al or 横断解析/al or 横断的研究/al or 横断的調査/al or 横断的評価/al or 横断的解析/al or クロスセクショナル研究/al or クロスセクショナル調査/al or クロスセクショナル評価/al or クロスセクショナル解析/al or クロス・セクショナル研究/al or クロス・セクショナル調査/al or クロス・セクショナル評価/al or クロス・セクショナル解析/al or 縦断研究/al or 縦断調査/al or 縦断評価/al or 縦断解析/al or 縦断的研究/al or 縦断的調査/al or 縦断的評価/al or 縦断的解析/al or 追跡研究/al or 追跡調査/al or 追跡評価/al or 追跡解析/al or 追跡的研究/al or 追跡的調査/al or 追跡的評価/al or 追跡的解析/al or 前向き/al or プロスペクティブ/al or 前方視/al or 後ろ向き/al or 後向き/al or レトロスペクティブ/al or 後方視/al or "Observational Study"/al or "cross-sectional Study"/al or "longitudinal

	study"/al or prospectiv/al or retrospectiv/al [215,395 件] #8 臨床試験/TH or 多施設共同研究/TH or 多施設/al or マルチセンタ/al or マルチ・センタ/al or 大規模臨床/al or バリデーション/al or メガトライアル/al or メガスタディ/al or 治験/al or 臨床試験/al or 臨床薬理試験/al or 評価試験/AL or 確認試験/al or 検証試験/al or 妥当性試験/al or 大規模試験/al or 臨床研究/al or 臨床薬理研究/al or 評価研究/AL or 確認研究/al or 検証研究/al or 妥当性研究/al or 大規模研究/al or Multicenter/al or Multi-center/al or Multicentre/al or Multi-centre/al or "clinical stud"/al or "Evaluation stud"/al or "Validation stud"/al or "mega stud"/al or "clinical trial"/al or "Evaluation trial"/al or "Validation trial"/al or "mega trial"/al [288,517 件] #9 製造販売後調査/TH or 市販後/AL or 市販直後/AL or 販売後/AL or 販売直後/AL or 製造販売後/AL or (製造販売後調査/TH or 特別調査/AL) or 使用成績/AL or 利用成績/AL or 医薬品再評価/al or "Post Market"/AL or Post-Market/AL or PostMarket/AL or EPPV/AL or フェーズ 4/AL or フェーズ-4/AL or フェーズ IV/AL or PHASE4/AL or PHASE-4/AL or "PHASE 4"/AL or PHASE-IV/AL or fourth-PHASE/AL or "PHASE IV"/AL or "fourth PHASE"/AL or 第 IV 相/AL or 第 4 相/AL or 第四相/AL or 臨床第 4/AL or 臨床第 IV/AL or 臨床第四/AL [13,652 件] #10 #1 and (#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9) [128 件] #11 (#10) and (PDAT=2013/6/1:2022/6/17 or IDAT=2013/6/1:2022/6/17) and (DT=2013:2022) [75 件] #12 ((#11 and (CK=ヒト or ヒト/TH or 人間/TH)) or (#11 not (CK=動物 or 動物/TH))) and (PT=原著論文,会議録,症例検討会) [51 件] #13 血液凝固異常/TH or 凝固障害/al or 凝固因子障害/al or 凝固異常/al or 凝固因子異常/al or "Blood Coagulation Disorder"/al or "Blood Coagulation Factor Disorder"/AL or Coagulopathy/al [62,259 件] #14 #12 and #13 [3 件]

MEDLINE	L1 3497 SEA HYDROXYETHYL STARCH DERIVATIVES+NT/CT L2 4797 SEA VOLUVEN? OR HES130? OR HES70? OR (HYDROXYETHYL OR HYDROXY(W)ETHYL)(W)STARCH? OR HES(2A)(130? OR 70?) OR SALINHES? OR HESPAN# L3 1671969 SEA RANDOMIZED CONTROLLED TRIAL?/DT OR PRAGMATIC CLINICAL TRIAL/DT OR RANDOM ALLOCATION+NT/CT OR (SINGLE-BLIND METHOD+NT OR DOUBLE-BLIND METHOD+NT)/CT OR (SINGL? OR DOUBLE? OR TREBL? OR TRIPL?)(W)(BLIND? OR MASK?) OR RANDOM? OR PRAGMATIC?(3W)(STUD? OR TRIAL? OR TEST?) OR PLACEBO? OR RCT L4 3260039 SEA COMPARATIVE STUDY/DT OR CONTROLLED CLINICAL TRIAL?/DT OR (CROSS-OVER STUDIES+NT OR MATCHED-PAIR ANALYSIS+NT)/CT OR (COMPARATIVE? OR COMPARE? OR COMPARIS? OR CONTROLLED OR CROSS(1W)OVER? OR CROSSOVER? OR MATCH?(W)PAIR)(3A)(STUD? OR TRIAL? OR TEST? OR DRUG? OR EVALUAT? OR ANALYS?) L5 242122 SEA (CLINICAL TRIAL, PHASE II OR CLINICAL TRIAL, PHASE III OR CLINICAL TRIAL, PHASE IV)/DT OR PHASE(1A)(1 OR I OR 1ST OR FIRST OR 2 OR II OR 2ND OR SECOND OR 3 OR III OR 3RD OR THIRD OR 4 OR IV OR FOURTH OR 4TH) L6 13341 SEA PHASE1 OR PHASEI OR PHASE2 OR PHASEII OR PHASE3 OR PHASEIII OR PHASE4 OR PHASEIV OR POSTMARKET? OR POST(1W)MARKET? L7 107504 SEA INTERVENTION?(3A)(STUD? OR TRIAL? OR TEST?) L8 2962998 SEA (COHORT STUDIES+NT OR CASE-CONTROL STUDIES+NT)/CT OR COHORT? OR CASE(1W)(CONTROL? OR BASE? OR COMPAR? OR REFER?)

	L9 2841736 SEA OBSERVATIONAL STUDY?/DT OR CROSS-SECTIONAL STUDIES+NT/CT OR (OBSERV? OR NON(1W)EXPERIMENT? OR NONEXPERIMENT? OR CROSS(1W)SECTION? OR CROSSSECTION? OR LONGITUDINAL? OR PROSPECTIVE? OR RETROSPECTIVE?)(3A)(STUD? OR TRIAL? OR TEST? OR SURVEY? OR DESIGN? OR RESEARCH? OR EVALUAT? OR ANALYS?) L10 1486916 SEA (CLINICAL STUDY OR CLINICAL TRIAL? OR EVALUATION STUDY OR MULTICENTER STUDY OR VALIDATION STUDY)/DT L11 2417283 SEA (CLINICAL? OR EVALUAT? OR MULTICENT? OR MULTI(W)CENT? OR LARGE(W)SCALE OR VALIDATION?)(3A)(STUD? OR TRIAL? OR TEST? OR SURVEY? OR DESIGN? OR RESEARCH? OR EVALUAT? OR ANALYS?) OR MEGA(W)(STUD? OR TRIAL?) OR MEGASTUD? OR MEGATRIAL? L12 696 SEA (L1 OR L2) AND (L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10) AND (20130601-20220617/ED OR 20130601-20220617/UP) AND 2013-2022/PY L13 437 SEA (L12/HUMAN OR (L12 NOT ANIMALS/CT)) NOT REVIEW/DT AND ARTICLE/DT L14 102949 SEA BLOOD COAGULATION DISORDERS+NT/CT L15 36018 SEA COAGULAT?(2A)(DISORDER? OR DEFICIEN?) OR COAGULOPATH? L16 19 SEA L13 AND (L14 OR L15) D L16 ALL 1-19

Appendix 4-5 Patients with thermal burn

Ichushi	#1 "Hydroxyethyl Starch Derivatives"/TH or "HES 130-0.4"/TH or ボルベン/al or VOLUVEN/al or サリンヘス/al or ヘスパンダー/al or Salinhes/al or Hespan/al or Hydroxyethylstarch/al or Hydroxyethyl-starch/al or "Hydroxyethyl starch"/al or ヒドロキシエチルスターチ/al or ヒドロキシエチル澱粉/al or "HES 130"/al or HES-130/al or HES130/al or "HES 70"/al or HES-70/al or HES70/al [939 件] #2 RD=ランダム化比較試験 or RD=準ランダム化比較試験 or ランダム化比較試験/TH or 準ランダム化比較試験/TH or ランダム割付け/TH or 一重盲検法/TH or 二重盲検法/TH or プラセボ/TH or ランダム/al or ランダマイ/al or 無作為/al or 盲検/al or ブラインド/al or シングルマスク/al or シングル・マスク/al or ダブルマスク/al or ダブル・マスク/al or トリプルマスク/al or トリプル・マスク/al or 実際的試験/al or 実際的研究/al or 実践的試験/al or 実践的研究/al or 実用的試験/al or 実用的研究/al or 実際的臨床試験/al or 実際的臨床研究/al or 実践的臨床試験/al or 実践的臨床研究/al or 実用的臨床試験/al or 実用的臨床研究/al or プラグマティック試験/al or プラグマティック研究/al or プラグマチック試験/al or プラグマチック研究/al or プラセボ/al or プラシーボ/al or 偽薬/al or 偽剤/al or RANDOM/al or BLIND/al or "SINGLE MASK"/al or SINGLE-MASK/al or "DOUBLE MASK"/al or DOUBLE-MASK/al or "TRIPLE MASK"/al or TRIPLE-MASK/al or "TREBLE MASK"/al or TREBLE-MASK/al or "pragmatic trial"/al or "pragmatic clinical trial"/al or "pragmatic stud"/al or "pragmatic clinical stud"/al or PLACEBO/al or RCT/al [100,693 件] #3 RD=比較研究 or 比較試験/AL or 比較臨床試験/AL or 比較薬理試験/AL or 比較研究/AL or 比較臨床研究/AL or 比較薬理研究/AL or クロスオーバー研究/TH or クロスオーバ/al or クロス・オーバ/AL or 交差試験/AL or 交差研究/AL or 交叉試験/AL or マッチドペア/al or 交叉研究/AL or COMPARAT/al or COMPARE/al or COMPARIS/al or "CROSS OVER"/AL or CROSSOVER/AL or CROSS-OVER/AL or "Matched Pair"/al or Matched-Pair/al [284,133 件] #4 第 II 相試験/TH or 第 III 相試験/TH or 第 2 相/AL or 第 II 相/AL or 第二相/AL or フェーズ 2/AL or Phase2/AL or "Phase 2"/AL or フェーズ II/AL or "フェーズ II"/AL or PhaseII/AL or "Phase II"/AL or 第 3 相/AL or 第 III 相/AL or 第三相/AL or フェーズ 3/AL or Phase3/AL

	or "Phase 3"/AL or フェーズ III/AL or "フェーズ III"/AL or PhaseIII/AL or "Phase III"/AL or 用量設定試験/al or 用量反応試験/al or 薬量設定試験/al or 薬量反応試験/al or 投与量設定試験/al or 投与量反応試験/al [20,447 件] #5 介入試験/al or 介入研究/al or 介入調査/al or 介入的試験/al or 介入的研究/al or 介入的調査/al or "intervention stud"/al or "interventional stud"/al or "intervention trial"/al or "interventional trial"/al or intervention-stud/al or interventional-stud/al or intervention-trial/al or interventional-trial/al [5,992 件] #6 コホート研究/TH or 症例対照研究/TH or コホート/al or コーホート/al or コウホート/al or Cohort/al or 症例対照/al or 症例-対照/al or 症例・対照/al or 症例コントロール/al or 患者対照/al or 患者-対照/al or 患者・対照/al or 患者コントロール/al or ケースコントロール/al or ケース-コントロール/al or ケース・コントロール/al or ケースベース/al or ケース-ベース/al or ケース・ベース/al or ケースリファレン/al or ケース-リファレン/al or ケース・リファレン/al or ケースレファレン/al or ケース-レファレン/al or ケース・レファレン/al or "Case Control"/al or Case-Control/al or "Case Base"/al or Case-Base/al or "Case Compar"/al or Case-Compar/al or "Case Referen"/al or Case-Referen/al [31,382 件] #7 観察研究/TH or 観察研究/al or 観察試験/al or 観察調査/al or 観察的研究/al or 観察的試験/al or 観察的調査/al or 断面研究/al or 断面調査/al or 断面評価/al or 断面解析/al or 断面的研究/al or 断面的調査/al or 断面的評価/al or 断面的解析/al or 横断研究/al or 横断調査/al or 横断評価/al or 横断解析/al or 横断的研究/al or 横断的調査/al or 横断的評価/al or 横断的解析/al or クロスセクショナル研究/al or クロスセクショナル調査/al or クロスセクショナル評価/al or クロスセクショナル解析/al or クロス・セクショナル研究/al or クロス・セクショナル調査/al or クロス・セクショナル評価/al or クロス・セクショナル解析/al or 縦断研究/al or 縦断調査/al or 縦断評価/al or 縦断解析/al or 縦断的研究/al or 縦断的調査/al or 縦断的評価/al or 縦断的解析/al or 追跡研究/al or 追跡調査/al or 追跡評価/al or 追跡解析/al or 追跡的研究/al or 追跡的調査/al or 追跡的評価/al or 追跡的解析/al or 前向き/al or プロスペクティブ/al or 前方視/al or 後ろ向き/al or 後向き/al or レトロスペクティブ/al or 後方視/al or "Observational Study"/al or "cross-sectional Study"/al or "longitudinal

	study"/al or prospectiv/al or retrospectiv/al [215,395 件] #8 臨床試験/TH or 多施設共同研究/TH or 多施設/al or マルチセンタ/al or マルチ・センタ/al or 大規模臨床/al or バリデーション/al or メガトライアル/al or メガスタディ/al or 治験/al or 臨床試験/al or 臨床薬理試験/al or 評価試験/AL or 確認試験/al or 検証試験/al or 妥当性試験/al or 大規模試験/al or 臨床研究/al or 臨床薬理研究/al or 評価研究/AL or 確認研究/al or 検証研究/al or 妥当性研究/al or 大規模研究/al or Multicenter/al or Multi-center/al or Multicentre/al or Multi-centre/al or "clinical stud"/al or "Evaluation stud"/al or "Validation stud"/al or "mega stud"/al or "clinical trial"/al or "Evaluation trial"/al or "Validation trial"/al or "mega trial"/al [288,517 件] #9 製造販売後調査/TH or 市販後/AL or 市販直後/AL or 販売後/AL or 販売直後/AL or 製造販売後/AL or (製造販売後調査/TH or 特別調査/AL) or 使用成績/AL or 利用成績/AL or 医薬品再評価/al or "Post Market"/AL or Post-Market/AL or PostMarket/AL or EPPV/AL or フェーズ 4/AL or フェーズ-4/AL or フェーズ IV/AL or PHASE4/AL or PHASE-4/AL or "PHASE 4"/AL or PHASE-IV/AL or fourth-PHASE/AL or "PHASE IV"/AL or "fourth PHASE"/AL or 第 IV 相/AL or 第 4 相/AL or 第四相/AL or 臨床第 4/AL or 臨床第 IV/AL or 臨床第四/AL [13,652 件] #10 #1 and (#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9) [128 件] #11 (#10) and (PDAT=2013/6/1:2022/6/17 or IDAT=2013/6/1:2022/6/17) and (DT=2013:2022) [75 件] #12 ((#11 and (CK=ヒト or ヒト/TH or 人間/TH)) or (#11 not (CK=動物 or 動物/TH))) and (PT=原著論文,会議録,症例検討会) [51 件] #13 熱傷/TH or 熱傷/AL or やけど/AL or 温熱性外傷/AL or 温熱性損傷/AL or 熱損傷/AL or 熱焼創/AL or BURN/ta [29,783 件] #14 #12 and #13 [0 件]

MEDLINE	L1 3497 SEA HYDROXYETHYL STARCH DERIVATIVES+NT/CT L2 4797 SEA VOLUVEN? OR HES130? OR HES70? OR (HYDROXYETHYL OR HYDROXY(W)ETHYL)(W)STARCH? OR HES(2A)(130? OR 70?) OR SALINHES? OR HESPAN# L3 1671969 SEA RANDOMIZED CONTROLLED TRIAL?/DT OR PRAGMATIC CLINICAL TRIAL/DT OR RANDOM ALLOCATION+NT/CT OR (SINGLE-BLIND METHOD+NT OR DOUBLE-BLIND METHOD+NT)/CT OR (SINGL? OR DOUBLE? OR TREBL? OR TRIPL?)(W)(BLIND? OR MASK?) OR RANDOM? OR PRAGMATIC?(3W)(STUD? OR TRIAL? OR TEST?) OR PLACEBO? OR RCT L4 3260039 SEA COMPARATIVE STUDY/DT OR CONTROLLED CLINICAL TRIAL?/DT OR (CROSS-OVER STUDIES+NT OR MATCHED-PAIR ANALYSIS+NT)/CT OR (COMPARATIVE? OR COMPARE? OR COMPARIS? OR CONTROLLED OR CROSS(1W)OVER? OR CROSSOVER? OR MATCH?(W)PAIR)(3A)(STUD? OR TRIAL? OR TEST? OR DRUG? OR EVALUAT? OR ANALYS?) L5 242122 SEA (CLINICAL TRIAL, PHASE II OR CLINICAL TRIAL, PHASE III OR CLINICAL TRIAL, PHASE IV)/DT OR PHASE(1A)(1 OR I OR 1ST OR FIRST OR 2 OR II OR 2ND OR SECOND OR 3 OR III OR 3RD OR THIRD OR 4 OR IV OR FOURTH OR 4TH) L6 13341 SEA PHASE1 OR PHASEI OR PHASE2 OR PHASEII OR PHASE3 OR PHASEIII OR PHASE4 OR PHASEIV OR POSTMARKET? OR POST(1W)MARKET? L7 107504 SEA INTERVENTION?(3A)(STUD? OR TRIAL? OR TEST?) L8 2962998 SEA (COHORT STUDIES+NT OR CASE-CONTROL STUDIES+NT)/CT OR COHORT? OR CASE(1W)(CONTROL? OR BASE? OR COMPAR? OR REFER?)

	L9 2841736 SEA OBSERVATIONAL STUDY?/DT OR CROSS-SECTIONAL STUDIES+NT/CT OR (OBSERV? OR NON(1W)EXPERIMENT? OR NONEXPERIMENT? OR CROSS(1W)SECTION? OR CROSSSECTION? OR LONGITUDINAL? OR PROSPECTIVE? OR RETROSPECTIVE?)(3A)(STUD? OR TRIAL? OR TEST? OR SURVEY? OR DESIGN? OR RESEARCH? OR EVALUAT? OR ANALYS?) L10 1486916 SEA (CLINICAL STUDY OR CLINICAL TRIAL? OR EVALUATION STUDY OR MULTICENTER STUDY OR VALIDATION STUDY)/DT L11 2417283 SEA (CLINICAL? OR EVALUAT? OR MULTICENT? OR MULTI(W)CENT? OR LARGE(W)SCALE OR VALIDATION?)(3A)(STUD? OR TRIAL? OR TEST? OR SURVEY? OR DESIGN? OR RESEARCH? OR EVALUAT? OR ANALYS?) OR MEGA(W)(STUD? OR TRIAL?) OR MEGASTUD? OR MEGATRIAL? L12 696 SEA (L1 OR L2) AND (L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10) AND (20130601-20220617/ED OR 20130601-20220617/UP) AND 2013-2022/PY L13 437 SEA (L12/HUMAN OR (L12 NOT ANIMALS/CT)) NOT REVIEW/DT AND ARTICLE/DT L14 60940 SEA BURNS+NT/CT L15 139471 SEA BURN? OR (HEAT OR THERM?)(1A)(INJUR? OR TRAUMA) OR SCALD? L16 7 SEA L13 AND (L14 OR L15) D L16 ALL 1-7

Appendix 4-6 Patients with dehydration

Ichushi	#1 "Hydroxyethyl Starch Derivatives"/TH or "HES 130-0.4"/TH or ボルベン/al or VOLUVEN/al or サリンヘス/al or ヘスパンダー/al or Salinhes/al or Hespan/al or Hydroxyethylstarch/al or Hydroxyethyl-starch/al or "Hydroxyethyl starch"/al or ヒドロキシエチルスターチ/al or ヒドロキシエチル澱粉/al or "HES 130"/al or HES-130/al or HES130/al or "HES 70"/al or HES-70/al or HES70/al [939 件] #2 RD=ランダム化比較試験 or RD=準ランダム化比較試験 or ランダム化比較試験/TH or 準ランダム化比較試験/TH or ランダム割付け/TH or 一重盲検法/TH or 二重盲検法/TH or プラセボ/TH or ランダム/al or ランダマイ/al or 無作為/al or 盲検/al or ブラインド/al or シングルマスク/al or シングル・マスク/al or ダブルマスク/al or ダブル・マスク/al or トリプルマスク/al or トリプル・マスク/al or 実際的試験/al or 実際的研究/al or 実践的試験/al or 実践的研究/al or 実用的試験/al or 実用的研究/al or 実際的臨床試験/al or 実際的臨床研究/al or 実践的臨床試験/al or 実践的臨床研究/al or 実用的臨床試験/al or 実用的臨床研究/al or プラグマティック試験/al or プラグマティック研究/al or プラグマチック試験/al or プラグマチック研究/al or プラセボ/al or プラシーボ/al or 偽薬/al or 偽剤/al or RANDOM/al or BLIND/al or "SINGLE MASK"/al or SINGLE-MASK/al or "DOUBLE MASK"/al or DOUBLE-MASK/al or "TRIPLE MASK"/al or TRIPLE-MASK/al or "TREBLE MASK"/al or TREBLE-MASK/al or "pragmatic trial"/al or "pragmatic clinical trial"/al or "pragmatic stud"/al or "pragmatic clinical stud"/al or PLACEBO/al or RCT/al [100,693 件] #3 RD=比較研究 or 比較試験/AL or 比較臨床試験/AL or 比較薬理試験/AL or 比較研究/AL or 比較臨床研究/AL or 比較薬理研究/AL or クロスオーバー研究/TH or クロスオーバ/al or クロス・オーバ/AL or 交差試験/AL or 交差研究/AL or 交叉試験/AL or マッチドペア/al or 交叉研究/AL or COMPARAT/al or COMPARE/al or COMPARIS/al or "CROSS OVER"/AL or CROSSOVER/AL or CROSS-OVER/AL or "Matched Pair"/al or Matched-Pair/al [284,133 件] #4 第 II 相試験/TH or 第 III 相試験/TH or 第 2 相/AL or 第 II 相/AL or 第二相/AL or フェーズ 2/AL or Phase2/AL or "Phase 2"/AL or フェーズ II/AL or "フェーズ II"/AL or PhaseII/AL or "Phase II"/AL or 第 3 相/AL or 第 III 相/AL or 第三相/AL or フェーズ 3/AL or Phase3/AL

	or "Phase 3"/AL or フェーズ III/AL or "フェーズ III"/AL or PhaseIII/AL or "Phase III"/AL or 用量設定試験/al or 用量反応試験/al or 薬量設定試験/al or 薬量反応試験/al or 投与量設定試験/al or 投与量反応試験/al [20,447 件] #5 介入試験/al or 介入研究/al or 介入調査/al or 介入的試験/al or 介入的研究/al or 介入的調査/al or "intervention stud"/al or "interventional stud"/al or "intervention trial"/al or "interventional trial"/al or intervention-stud/al or interventional-stud/al or intervention-trial/al or interventional-trial/al [5,992 件] #6 コホート研究/TH or 症例対照研究/TH or コホート/al or コーホート/al or コウホート/al or Cohort/al or 症例対照/al or 症例-対照/al or 症例・対照/al or 症例コントロール/al or 患者対照/al or 患者-対照/al or 患者・対照/al or 患者コントロール/al or ケースコントロール/al or ケース-コントロール/al or ケース・コントロール/al or ケースベース/al or ケース-ベース/al or ケース・ベース/al or ケースリファレン/al or ケース-リファレン/al or ケース・リファレン/al or ケースレファレン/al or ケース-レファレン/al or ケース・レファレン/al or "Case Control"/al or Case-Control/al or "Case Base"/al or Case-Base/al or "Case Compar"/al or Case-Compar/al or "Case Referen"/al or Case-Referen/al [31,382 件] #7 観察研究/TH or 観察研究/al or 観察試験/al or 観察調査/al or 観察的研究/al or 観察的試験/al or 観察的調査/al or 断面研究/al or 断面調査/al or 断面評価/al or 断面解析/al or 断面的研究/al or 断面的調査/al or 断面的評価/al or 断面的解析/al or 横断研究/al or 横断調査/al or 横断評価/al or 横断解析/al or 横断的研究/al or 横断的調査/al or 横断的評価/al or 横断的解析/al or クロスセクショナル研究/al or クロスセクショナル調査/al or クロスセクショナル評価/al or クロスセクショナル解析/al or クロス・セクショナル研究/al or クロス・セクショナル調査/al or クロス・セクショナル評価/al or クロス・セクショナル解析/al or 縦断研究/al or 縦断調査/al or 縦断評価/al or 縦断解析/al or 縦断的研究/al or 縦断的調査/al or 縦断的評価/al or 縦断的解析/al or 追跡研究/al or 追跡調査/al or 追跡評価/al or 追跡解析/al or 追跡的研究/al or 追跡的調査/al or 追跡的評価/al or 追跡的解析/al or 前向き/al or プロスペクティブ/al or 前方視/al or 後ろ向き/al or 後向き/al or レトロスペクティブ/al or 後方視/al or "Observational Study"/al or "cross-sectional Study"/al or "longitudinal

	study"/al or prospectiv/al or retrospectiv/al [215,395 件] #8 臨床試験/TH or 多施設共同研究/TH or 多施設/al or マルチセンタ/al or マルチ・センタ/al or 大規模臨床/al or バリデーション/al or メガトライアル/al or メガスタディ/al or 治験/al or 臨床試験/al or 臨床薬理試験/al or 評価試験/AL or 確認試験/al or 検証試験/al or 妥当性試験/al or 大規模試験/al or 臨床研究/al or 臨床薬理研究/al or 評価研究/AL or 確認研究/al or 検証研究/al or 妥当性研究/al or 大規模研究/al or Multicenter/al or Multi-center/al or Multicentre/al or Multi-centre/al or "clinical stud"/al or "Evaluation stud"/al or "Validation stud"/al or "mega stud"/al or "clinical trial"/al or "Evaluation trial"/al or "Validation trial"/al or "mega trial"/al [288,517 件] #9 製造販売後調査/TH or 市販後/AL or 市販直後/AL or 販売後/AL or 販売直後/AL or 製造販売後/AL or (製造販売後調査/TH or 特別調査/AL) or 使用成績/AL or 利用成績/AL or 医薬品再評価/al or "Post Market"/AL or Post-Market/AL or PostMarket/AL or EPPV/AL or フェーズ 4/AL or フェーズ-4/AL or フェーズ IV/AL or PHASE4/AL or PHASE-4/AL or "PHASE 4"/AL or PHASE-IV/AL or fourth-PHASE/AL or "PHASE IV"/AL or "fourth PHASE"/AL or 第 IV 相/AL or 第 4 相/AL or 第四相/AL or 臨床第 4/AL or 臨床第 IV/AL or 臨床第四/AL [13,652 件] #10 #1 and (#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9) [128 件] #11 (#10) and (PDAT=2013/6/1:2022/6/17 or IDAT=2013/6/1:2022/6/17) and (DT=2013:2022) [75 件] #12 ((#11 and (CK=ヒト or ヒト/TH or 人間/TH)) or (#11 not (CK=動物 or 動物/TH))) and (PT=原著論文,会議録,症例検討会) [51 件] #13 脱水症/TH or 脱水/AL or 水欠症/AL or DEHYDRAT/al or Anhydrat/al [20,724 件] #14 #12 and #13 [0 件]

MEDLINE	L1 3497 SEA HYDROXYETHYL STARCH DERIVATIVES+NT/CT L2 4797 SEA VOLUVEN? OR HES130? OR HES70? OR (HYDROXYETHYL OR HYDROXY(W)ETHYL)(W)STARCH? OR HES(2A)(130? OR 70?) OR SALINHES? OR HESPAN# L3 1671969 SEA RANDOMIZED CONTROLLED TRIAL?/DT OR PRAGMATIC CLINICAL TRIAL/DT OR RANDOM ALLOCATION+NT/CT OR (SINGLE-BLIND METHOD+NTOR DOUBLE-BLIND METHOD+NT)/CT OR (SINGL? OR DOUBLE? OR TREBL? OR TRIPL?)(W)(BLIND? OR MASK?) OR RANDOM? OR PRAGMATIC?(3W)(STUD? OR TRIAL? OR TEST?) OR PLACEBO? OR RCT L4 3260039 SEA COMPARATIVE STUDY/DT OR CONTROLLED CLINICAL TRIAL?/DT OR (CROSS-OVER STUDIES+NT OR MATCHED-PAIR ANALYSIS+NT)/CT OR (COMPARATIVE? OR COMPARE? OR COMPARIS? OR CONTROLLED OR CROSS(1W)OVER? OR CROSSOVER? OR MATCH?(W)PAIR)(3A)(STUD? OR TRIAL? OR TEST? OR DRUG? OR EVALUAT? OR ANALYS?) L5 242122 SEA (CLINICAL TRIAL, PHASE II OR CLINICAL TRIAL, PHASE III OR CLINICAL TRIAL, PHASE IV)/DT OR PHASE(1A)(1 OR I OR 1ST OR FIRST OR 2 OR II OR 2ND OR SECOND OR 3 OR III OR 3RD OR THIRD OR 4 OR IV OR FOURTH OR 4TH) L6 13341 SEA PHASE1 OR PHASEI OR PHASE2 OR PHASEII OR PHASE3 OR PHASEIII OR PHASE4 OR PHASEIV OR POSTMARKET? OR POST(1W)MARKET? L7 107504 SEA INTERVENTION?(3A)(STUD? OR TRIAL? OR TEST?) L8 2962998 SEA (COHORT STUDIES+NT OR CASE-CONTROL STUDIES+NT)/CT OR COHORT? OR CASE(1W)(CONTROL? OR BASE? OR COMPAR? OR REFER?)

	L9 2841736 SEA OBSERVATIONAL STUDY?/DT OR CROSS-SECTIONAL STUDIES+NT/CT OR (OBSERV? OR NON(1W)EXPERIMENT? OR NONEXPERIMENT? OR CROSS(1W)SECTION? OR CROSSSECTION? OR LONGITUDINAL? OR PROSPECTIVE? OR RETROSPECTIVE?)(3A)(STUD? OR TRIAL? OR TEST? OR SURVEY? OR DESIGN? OR RESEARCH? OR EVALUAT? OR ANALYS?) L10 1486916 SEA (CLINICAL STUDY OR CLINICAL TRIAL? OR EVALUATION STUDY OR MULTICENTER STUDY OR VALIDATION STUDY)/DT L11 2417283 SEA (CLINICAL? OR EVALUAT? OR MULTICENT? OR MULTI(W)CENT? OR LARGE(W)SCALE OR VALIDATION?)(3A)(STUD? OR TRIAL? OR TEST? OR SURVEY? OR DESIGN? OR RESEARCH? OR EVALUAT? OR ANALYS?) OR MEGA(W)(STUD? OR TRIAL?) OR MEGASTUD? OR MEGATRIAL? L12 696 SEA (L1 OR L2) AND (L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10) AND (20130601-20220617/ED OR 20130601-20220617/UP) AND 2013-2022/PY L13 437 SEA (L12/HUMAN OR (L12 NOT ANIMALS/CT)) NOT REVIEW/DT AND ARTICLE/DT L14 14243 SEA DEHYDRATION+NT/CT L15 55931 SEA DEHYDRAT? OR ANHYDRAT? L16 6 SEA L13 AND (L14 OR L15) D L16 ALL 1-6

Appendix 4-7 Organ transplant patients

Ichushi	#1 "Hydroxyethyl Starch Derivatives"/TH or "HES 130-0.4"/TH or ボルベン/al or VOLUVEN/al or サリンヘス/al or ヘスパンダー/al or Salinhes/al or Hespan/al or Hydroxyethylstarch/al or Hydroxyethyl-starch/al or "Hydroxyethyl starch"/al or ヒドロキシエチルスターチ/al or ヒドロキシエチル澱粉/al or "HES 130"/al or HES-130/al or HES130/al or "HES 70"/al or HES-70/al or HES70/al [939 件] #2 RD=ランダム化比較試験 or RD=準ランダム化比較試験 or ランダム化比較試験/TH or 準ランダム化比較試験/TH or ランダム割付け/TH or 一重盲検法/TH or 二重盲検法/TH or プラセボ/TH or ランダム/al or ランダマイ/al or 無作為/al or 盲検/al or ブラインド/al or シングルマスク/al or シングル・マスク/al or ダブルマスク/al or ダブル・マスク/al or トリプルマスク/al or トリプル・マスク/al or 実際的試験/al or 実際的研究/al or 実践的試験/al or 実践的研究/al or 実用的試験/al or 実用的研究/al or 実際的臨床試験/al or 実際的臨床研究/al or 実践的臨床試験/al or 実践的臨床研究/al or 実用的臨床試験/al or 実用的臨床研究/al or プラグマティック試験/al or プラグマティック研究/al or プラグマチック試験/al or プラグマチック研究/al or プラセボ/al or プラシーボ/al or 偽薬/al or 偽剤/al or RANDOM/al or BLIND/al or "SINGLE MASK"/al or SINGLE-MASK/al or "DOUBLE MASK"/al or DOUBLE-MASK/al or "TRIPLE MASK"/al or TRIPLE-MASK/al or "TREBLE MASK"/al or TREBLE-MASK/al or "pragmatic trial"/al or "pragmatic clinical trial"/al or "pragmatic stud"/al or "pragmatic clinical stud"/al or PLACEBO/al or RCT/al [100,693 件] #3 RD=比較研究 or 比較試験/AL or 比較臨床試験/AL or 比較薬理試験/AL or 比較研究/AL or 比較臨床研究/AL or 比較薬理研究/AL or クロスオーバー研究/TH or クロスオーバ/al or クロス・オーバ/AL or 交差試験/AL or 交差研究/AL or 交叉試験/AL or マッチドペア/al or 交叉研究/AL or COMPARAT/al or COMPARE/al or COMPARIS/al or "CROSS OVER"/AL or CROSSOVER/AL or CROSS-OVER/AL or "Matched Pair"/al or Matched-Pair/al [284,133 件] #4 第 II 相試験/TH or 第 III 相試験/TH or 第 2 相/AL or 第 II 相/AL or 第二相/AL or フェーズ 2/AL or Phase2/AL or "Phase 2"/AL or フェーズ II/AL or "フェーズ II"/AL or PhaseII/AL or "Phase II"/AL or 第 3 相/AL or 第 III 相/AL or 第三相/AL or フェーズ 3/AL or Phase3/AL

	or "Phase 3"/AL or フェーズ III/AL or "フェーズ III"/AL or PhaseIII/AL or "Phase III"/AL or 用量設定試験/al or 用量反応試験/al or 薬量設定試験/al or 薬量反応試験/al or 投与量設定試験/al or 投与量反応試験/al [20,447 件] #5 介入試験/al or 介入研究/al or 介入調査/al or 介入的試験/al or 介入的研究/al or 介入的調査/al or "intervention stud"/al or "interventional stud"/al or "intervention trial"/al or "interventional trial"/al or intervention-stud/al or interventional-stud/al or intervention-trial/al or interventional-trial/al [5,992 件] #6 コホート研究/TH or 症例対照研究/TH or コホート/al or コーホート/al or コウホート/al or Cohort/al or 症例対照/al or 症例-対照/al or 症例・対照/al or 症例コントロール/al or 患者対照/al or 患者-対照/al or 患者・対照/al or 患者コントロール/al or ケースコントロール/al or ケース-コントロール/al or ケース・コントロール/al or ケースベース/al or ケース-ベース/al or ケース・ベース/al or ケースリファレン/al or ケース-リファレン/al or ケース・リファレン/al or ケースレファレン/al or ケース-レファレン/al or ケース・レファレン/al or "Case Control"/al or Case-Control/al or "Case Base"/al or Case-Base/al or "Case Compar"/al or Case-Compar/al or "Case Referen"/al or Case-Referen/al [31,382 件] #7 観察研究/TH or 観察研究/al or 観察試験/al or 観察調査/al or 観察的研究/al or 観察的試験/al or 観察的調査/al or 断面研究/al or 断面調査/al or 断面評価/al or 断面解析/al or 断面的研究/al or 断面的調査/al or 断面的評価/al or 断面的解析/al or 横断研究/al or 横断調査/al or 横断評価/al or 横断解析/al or 横断的研究/al or 横断的調査/al or 横断的評価/al or 横断的解析/al or クロスセクショナル研究/al or クロスセクショナル調査/al or クロスセクショナル評価/al or クロスセクショナル解析/al or クロス・セクショナル研究/al or クロス・セクショナル調査/al or クロス・セクショナル評価/al or クロス・セクショナル解析/al or 縦断研究/al or 縦断調査/al or 縦断評価/al or 縦断解析/al or 縦断的研究/al or 縦断的調査/al or 縦断的評価/al or 縦断的解析/al or 追跡研究/al or 追跡調査/al or 追跡評価/al or 追跡解析/al or 追跡的研究/al or 追跡的調査/al or 追跡的評価/al or 追跡的解析/al or 前向き/al or プロスペクティブ/al or 前方視/al or 後ろ向き/al or 後向き/al or レトロスペクティブ/al or 後方視/al or "Observational Study"/al or "cross-sectional Study"/al or "longitudinal

	study"/al or prospectiv/al or retrospectiv/al [215,395 件] #8 臨床試験/TH or 多施設共同研究/TH or 多施設/al or マルチセンタ/al or マルチ・センタ/al or 大規模臨床/al or バリデーション/al or メガトライアル/al or メガスタディ/al or 治験/al or 臨床試験/al or 臨床薬理試験/al or 評価試験/AL or 確認試験/al or 検証試験/al or 妥当性試験/al or 大規模試験/al or 臨床研究/al or 臨床薬理研究/al or 評価研究/AL or 確認研究/al or 検証研究/al or 妥当性研究/al or 大規模研究/al or Multicenter/al or Multi-center/al or Multicentre/al or Multi-centre/al or "clinical stud"/al or "Evaluation stud"/al or "Validation stud"/al or "mega stud"/al or "clinical trial"/al or "Evaluation trial"/al or "Validation trial"/al or "mega trial"/al [288,517 件] #9 製造販売後調査/TH or 市販後/AL or 市販直後/AL or 販売後/AL or 販売直後/AL or 製造販売後/AL or (製造販売後調査/TH or 特別調査/AL) or 使用成績/AL or 利用成績/AL or 医薬品再評価/al or "Post Market"/AL or Post-Market/AL or PostMarket/AL or EPPV/AL or フェーズ 4/AL or フェーズ-4/AL or フェーズ IV/AL or PHASE4/AL or PHASE-4/AL or "PHASE 4"/AL or PHASE-IV/AL or fourth-PHASE/AL or "PHASE IV"/AL or "fourth PHASE"/AL or 第 IV 相/AL or 第 4 相/AL or 第四相/AL or 臨床第 4/AL or 臨床第 IV/AL or 臨床第四/AL [13,652 件] #10 #1 and (#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9) [128 件] #11 (#10) and (PDAT=2013/6/1:2022/6/17 or IDAT=2013/6/1:2022/6/17) and (DT=2013:2022) [75 件] #12 ((#11 and (CK=ヒト or ヒト/TH or 人間/TH)) or (#11 not (CK=動物 or 動物/TH))) and (PT=原著論文,会議録,症例検討会) [51 件] #13 臓器移植/TH or 臓器保存/TH or 臓器移植/al or 臓器グラフト/al or 腎移植/al or 肺移植/al or (心臓移植/TH or 心移植/AL) or (肝臓移植/TH or 肝移植/AL) or 腸移植/al or 膵移植/al or 腎臓移植/al or 心臓移植/al or 肝臓移植/al or 膵臓移植/al or 移植腎/al or 移植肺/al or 移植心/al or 移植肝/al or 移植腸/al or 移植膵/al or 腎グラフト/al or 肺グラフト/al or 心グラフト/al or 肝グラフト/al or 腸グラフト/al or 膵グラフト/al or ("移植片"/TH or "organ transplant"/AL) or "organ graft"/al or "renal transplant"/al or "kidney transplant"/al or "renal

	graft"/al or "kidney graft"/al or "lung transplant"/al or "pulmonary transplant"/al or "lung graft"/al or "pulmonary graft"/al or "cardiac transplant"/al or "heart transplant"/al or "cardiac graft"/al or "heart graft"/al or "liver transplant"/al or "liver graft"/al or "hepatic transplant"/al or "hepatic graft"/al or "bowel transplant"/al or "pancreas transplant"/al or "pancreas graft"/al [108,628 件] #14 #12 and #13 [1 件]
MEDLINE	L1 3497 SEA HYDROXYETHYL STARCH DERIVATIVES+NT/CT L2 4797 SEA VOLUVEN? OR HES130? OR HES70? OR (HYDROXYETHYL OR HYDROXY(W)ETHYL)(W)STARCH? OR HES(2A)(130? OR 70?) OR SALINHES? OR HESPAN# L3 1672479 SEA RANDOMIZED CONTROLLED TRIAL?/DT OR PRAGMATIC CLINICAL TRIAL/DT OR RANDOM ALLOCATION+NT/CT OR (SINGLE-BLIND METHOD+NT OR DOUBLE-BLIND METHOD+NT)/CT OR (SINGL? OR DOUBLE? OR TREBL? OR TRIPL?)(W)(BLIND? OR MASK?) OR RANDOM? OR PRAGMATIC?(3W)(STUD? OR TRIAL? OR TEST?) OR PLACEBO? OR RCT L4 3260595 SEA COMPARATIVE STUDY/DT OR CONTROLLED CLINICAL TRIAL?/DT OR (CROSS-OVER STUDIES+NT OR MATCHED-PAIR ANALYSIS+NT)/CT OR (COMPARATIVE? OR COMPARE? OR COMPARIS? OR CONTROLLED OR CROSS(1W)OVER? OR CROSSOVER? OR MATCH?(W)PAIR)(3A)(STUD? OR TRIAL? OR TEST? OR DRUG? OR EVALUAT? OR ANALYS?) L5 242170 SEA (CLINICAL TRIAL, PHASE II OR CLINICAL TRIAL, PHASE III OR CLINICAL TRIAL, PHASE IV)/DT OR PHASE(1A)(1 OR I OR 1ST OR FIRST OR 2 OR II OR 2ND OR SECOND OR 3 OR III OR 3RD OR THIRD OR 4 OR IV OR FOURTH OR 4TH) L6 13343 SEA PHASE1 OR PHASEI OR PHASE2 OR PHASEII OR PHASE3 OR PHASEIII OR PHASE4 OR PHASEIV OR

	POSTMARKET? OR POST(1W)MARKET? L7 107563 SEA INTERVENTION?(3A)(STUD? OR TRIAL? OR TEST?) L8 2964308 SEA (COHORT STUDIES+NT OR CASE-CONTROL STUDIES+NT)/CT OR COHORT? OR CASE(1W)(CONTROL? OR BASE? OR COMPAR? OR REFER?) L9 2843022 SEA OBSERVATIONAL STUDY?/DT OR CROSS-SECTIONAL STUDIES+NT/CT OR (OBSERV? OR NON(1W)EXPERIMENT? OR NONEXPERIMENT? OR CROSS(1W)SECTION? OR CROSSSECTION? OR LONGITUDINAL? OR PROSPECTIVE? OR RETROSPECTIVE?)(3A)(STUD? OR TRIAL? OR TEST? OR SURVEY? OR DESIGN? OR RESEARCH? OR EVALUAT? OR ANALYS?) L10 1487333 SEA (CLINICAL STUDY OR CLINICAL TRIAL? OR EVALUATION STUDY OR MULTICENTER STUDY OR VALIDATION STUDY)/DT L11 2418103 SEA (CLINICAL? OR EVALUAT? OR MULTICENT? OR MULTI(W)CENT? OR LARGE(W)SCALE OR VALIDATION?)(3A)(STUD? OR TRIAL? OR TEST? OR SURVEY? OR DESIGN? OR RESEARCH? OR EVALUAT? OR ANALYS?) OR MEGA(W)(STUD? OR TRIAL?) OR MEGASTUD? OR MEGATRIAL? L12 696 SEA (L1 OR L2) AND (L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10) AND (20130601-20220617/ED OR 20130601-20220617/UP) AND 2013-2022/PY L13 437 SEA (L12/HUMAN OR (L12 NOT ANIMALS/CT)) NOT REVIEW/DT AND ARTICLE/DT L14 318080 SEA ORGAN TRANSPLANTATION+NT/CT OR INTESTINES+NT/CT(L)TR/CT OR (ORGAN? OR RENAL? OR KIDNEY? OR HEART? OR CARDIAC? OR LIVER? OR HEPATIC? OR PANCRE? OR INTESTIN? OR BOWEL? OR LUNG OR PULMONARY)(3A)(TRANSPLANT? OR GRAFT?)

	L15 20 SEA L13 AND L14 D L15 ALL 1-20

Appendix 4-8 Patients with renal failure

Ichushi	"#1 ""Hydroxyethyl Starch Derivatives""/TH or ""HES 130-0.4""/TH or ボルベン/al or VOLUVEN/al or サリンヘス/al or ヘスパンダー/al or Salinhes/al or Hespan/al or Hydroxyethylstarch/al or Hydroxyethyl-starch/al or ""Hydroxyethyl starch""/al or ヒドロキシエチルスターチ/al or ヒドロキシエチル澱粉/al or ""HES 130""/al or HES-130/al or HES130/al or ""HES 70""/al or HES-70/al or HES70/al [939 件] #2 RD=ランダム化比較試験 or RD=準ランダム化比較試験 or ランダム化比較試験/TH or 準ランダム化比較試験/TH or ランダム割付け/TH or 一重盲検法/TH or 二重盲検法/TH or プラセボ/TH or ランダム/al or ランダマイ/al or 無作為/al or 盲検/al or ブラインド/al or シングルマスク/al or シングル・マスク/al or ダブルマスク/al or ダブル・マスク/al or トリプルマスク/al or トリプル・マスク/al or 実際的試験/al or 実際的研究/al or 実践的試験/al or 実践的研究/al or 実用的試験/al or 実用的研究/al or 実際的臨床試験/al or 実際的臨床研究/al or 実践的臨床試験/al or 実践的臨床研究/al or 実用的臨床試験/al or 実用的臨床研究/al or プラグマティック試験/al or プラグマティック研究/al or プラグマチック試験/al or プラグマチック研究/al or プラセボ/al or プラシーボ/al or 偽薬/al or 偽剤/al or RANDOM/al or BLIND/al or ""SINGLE MASK""/al or SINGLE-MASK/al or ""DOUBLE MASK""/al or DOUBLE-MASK/al or ""TRIPLE MASK""/al or TRIPLE-MASK/al or ""TREBLE MASK""/al or TREBLE-MASK/al or ""pragmatic trial""/al or ""pragmatic clinical trial""/al or ""pragmatic stud""/al or ""pragmatic clinical stud""/al or PLACEBO/al or RCT/al [100,693 件] #3 RD=比較研究 or 比較試験/AL or 比較臨床試験/AL or 比較薬理試験/AL or 比較研究/AL or 比較臨床研究/AL or 比較薬理研究/AL or クロスオーバー研究/TH or クロスオーバ/al or クロス・オーバ/AL or 交差試験/AL or 交差研究/AL or 交叉試験/AL or マッチドペア/al or 交叉研究/AL or COMPARAT/al or COMPARE/al or COMPARIS/al or ""CROSS OVER""/AL or CROSSOVER/AL or CROSS-OVER/AL or ""Matched Pair""/al or Matched-Pair/al [284,133 件] #4 第 II 相試験/TH or 第 III 相試験/TH or 第 2 相/AL or 第 II 相/AL or 第二相/AL or フェーズ 2/AL or Phase2/AL or ""Phase 2""/AL or フェーズ II/AL or ""フェーズ II""/AL or PhaseII/AL or ""Phase II""/AL or 第 3 相/AL or 第 III 相/AL or 第三相/AL or フェーズ 3/AL or

	Phase3/AL or ""Phase 3""/AL or フェーズ III/AL or ""フェーズ III""/AL or PhaseIII/AL or ""Phase III""/AL or 用量設定試験/al or 用量反応試験/al or 薬量設定試験/al or 薬量反応試験/al or 投与量設定試験/al or 投与量反応試験/al [20,447 件] #5 介入試験/al or 介入研究/al or 介入調査/al or 介入的試験/al or 介入的研究/al or 介入的調査/al or ""intervention stud""/al or ""interventional stud""/al or ""intervention trial""/al or ""interventional trial""/al or intervention-stud/al or interventional-stud/al or intervention-trial/al or interventional-trial/al [5,992 件] #6 コホート研究/TH or 症例対照研究/TH or コホート/al or コーホート/al or コウホート/al or Cohort/al or 症例対照/al or 症例-対照/al or 症例・対照/al or 症例コントロール/al or 患者対照/al or 患者-対照/al or 患者・対照/al or 患者コントロール/al or ケースコントロール/al or ケース-コントロール/al or ケース・コントロール/al or ケースベース/al or ケース-ベース/al or ケース・ベース/al or ケースリファレン/al or ケース-リファレン/al or ケース・リファレン/al or ケースレファレン/al or ケース-レファレン/al or ケース・レファレン/al or ""Case Control""/al or Case-Control/al or ""Case Base""/al or Case-Base/al or ""Case Compar""/al or Case-Compar/al or ""Case Referen""/al or Case-Referen/al [31,382 件] #7 観察研究/TH or 観察研究/al or 観察試験/al or 観察調査/al or 観察的研究/al or 観察的試験/al or 観察的調査/al or 断面研究/al or 断面調査/al or 断面評価/al or 断面解析/al or 断面的研究/al or 断面的調査/al or 断面的評価/al or 断面的解析/al or 横断研究/al or 横断調査/al or 横断評価/al or 横断解析/al or 横断的研究/al or 横断的調査/al or 横断的評価/al or 横断的解析/al or クロスセクショナル研究/al or クロスセクショナル調査/al or クロスセクショナル評価/al or クロスセクショナル解析/al or クロス・セクショナル研究/al or クロス・セクショナル調査/al or クロス・セクショナル評価/al or クロス・セクショナル解析/al or 縦断研究/al or 縦断調査/al or 縦断評価/al or 縦断解析/al or 縦断的研究/al or 縦断的調査/al or 縦断的評価/al or 縦断的解析/al or 追跡研究/al or 追跡調査/al or 追跡評価/al or 追跡解析/al or 追跡的研究/al or 追跡的調査/al or 追跡的評価/al or 追跡的解析/al or 前向き/al or プロスペクティブ/al or 前方視/al or 後ろ向き/al or 後向き/al or レトロスペクティブ/al or 後方視/al or ""Observational Study""/al or ""cross-sectional Study""/al or ""longitudinal

	study""/al or prospectiv/al or retrospectiv/al [215,395 件] #8 臨床試験/TH or 多施設共同研究/TH or 多施設/al or マルチセンタ/al or マルチ・センタ/al or 大規模臨床/al or バリデーション/al or メガトライアル/al or メガスタディ/al or 治験/al or 臨床試験/al or 臨床薬理試験/al or 評価試験/AL or 確認試験/al or 検証試験/al or 妥当性試験/al or 大規模試験/al or 臨床研究/al or 臨床薬理研究/al or 評価研究/AL or 確認研究/al or 検証研究/al or 妥当性研究/al or 大規模研究/al or Multicenter/al or Multi-center/al or Multicentre/al or Multi-centre/al or ""clinical stud""/al or ""Evaluation stud""/al or ""Validation stud""/al or ""mega stud""/al or ""clinical trial""/al or ""Evaluation trial""/al or ""Validation trial""/al or ""mega trial""/al [288,517 件] #9 製造販売後調査/TH or 市販後/AL or 市販直後/AL or 販売後/AL or 販売直後/AL or 製造販売後/AL or (製造販売後調査/TH or 特別調査/AL) or 使用成績/AL or 利用成績/AL or 医薬品再評価/al or ""Post Market""/AL or Post-Market/AL or PostMarket/AL or EPPV/AL or フェーズ4/AL or フェーズ-4/AL or フェーズIV/AL or PHASE4/AL or PHASE-4/AL or ""PHASE 4""/AL or PHASE-IV/AL or fourth-PHASE/AL or ""PHASE IV""/AL or ""fourth PHASE""/AL or 第 IV 相/AL or 第 4 相/AL or 第四相/AL or 臨床第 4/AL or 臨床第 IV/AL or 臨床第四/AL [13,652 件] #10 #1 and (#2 or #3 or #4 or #5 or #6 or #7 or #8 or #9) [128 件] #11 (#10) and (PDAT=2013/6/1:2022/6/17 or IDAT=2013/6/1:2022/6/17) and (DT=2013:2022) [75 件] #12 ((#11 and (CK=ヒト or ヒト/TH or 人間/TH)) or (#11 not (CK=動物 or 動物/TH))) and (PT=原著論文,会議録,症例検討会) [51 件] #13 脱水症/TH or 脱水/AL or 水欠症/AL or DEHYDRAT/al or Anhydrat/al [20,724 件] #14 #12 and #13 [0 件]"

MEDLINE	L1 3497 SEA HYDROXYETHYL STARCH DERIVATIVES+NT/CT L2 4797 SEA VOLUVEN? OR HES130? OR HES70? OR (HYDROXYETHYL OR HYDROXY(W)ETHYL)(W)STARCH? OR HES(2A)(130? OR 70?) OR SALINHES? OR HESPAN# L3 1671969 SEA RANDOMIZED CONTROLLED TRIAL?/DT OR PRAGMATIC CLINICAL TRIAL/DT OR RANDOM ALLOCATION+NT/CT OR (SINGLE-BLIND METHOD+NT OR DOUBLE-BLIND METHOD+NT)/CT OR (SINGL? OR DOUBLE? OR TREBL? OR TRIPL?)(W)(BLIND? OR MASK?) OR RANDOM? OR PRAGMATIC?(3W)(STUD? OR TRIAL? OR TEST?) OR PLACEBO? OR RCT L4 3260039 SEA COMPARATIVE STUDY/DT OR CONTROLLED CLINICAL TRIAL?/DT OR (CROSS-OVER STUDIES+NT OR MATCHED-PAIR ANALYSIS+NT)/CT OR (COMPARATIVE? OR COMPARE? OR COMPARIS? OR CONTROLLED OR CROSS(1W)OVER? OR CROSSOVER? OR MATCH?(W)PAIR)(3A)(STUD? OR TRIAL? OR TEST? OR DRUG? OR EVALUAT? OR ANALYS?) L5 242122 SEA (CLINICAL TRIAL, PHASE II OR CLINICAL TRIAL, PHASE III OR CLINICAL TRIAL, PHASE IV)/DT OR PHASE(1A)(1 OR I OR 1ST OR FIRST OR 2 OR II OR 2ND OR SECOND OR 3 OR III OR 3RD OR THIRD OR 4 OR IV OR FOURTH OR 4TH) L6 13341 SEA PHASE1 OR PHASEI OR PHASE2 OR PHASEII OR PHASE3 OR PHASEIII OR PHASE4 OR PHASEIV OR POSTMARKET? OR POST(1W)MARKET? L7 107504 SEA INTERVENTION?(3A)(STUD? OR TRIAL? OR TEST?) L8 2962998 SEA (COHORT STUDIES+NT OR CASE-CONTROL STUDIES+NT)/CT OR COHORT? OR CASE(1W)(CONTROL? OR BASE? OR COMPAR? OR REFER?) L9 2841736 SEA OBSERVATIONAL STUDY?/DT OR CROSS-SECTIONAL STUDIES+NT/CT OR (OBSERV? OR

	NON(1W)EXPERIMENT? OR NONEXPERIMENT? OR CROSS(1W)SECTION? OR CROSSSECTION? OR LONGITUDINAL? OR PROSPECTIVE? OR RETROSPECTIVE?)(3A)(STUD? OR TRIAL? OR TEST? OR SURVEY? OR DESIGN? OR RESEARCH? OR EVALUAT? OR ANALYS?) L10 1486916 SEA (CLINICAL STUDY OR CLINICAL TRIAL? OR EVALUATION STUDY OR MULTICENTER STUDY OR VALIDATION STUDY)/DT L11 2417283 SEA (CLINICAL? OR EVALUAT? OR MULTICENT? OR MULTI(W)CENT? OR LARGE(W)SCALE OR VALIDATION?)(3A)(STUD? OR TRIAL? OR TEST? OR SURVEY? OR DESIGN? OR RESEARCH? OR EVALUAT? OR ANALYS?) OR MEGA(W)(STUD? OR TRIAL?) OR MEGASTUD? OR MEGATRIAL? L12 696 SEA (L1 OR L2) AND (L3 OR L4 OR L5 OR L6 OR L7 OR L8 OR L9 OR L10) AND (20130601-20220617/ED OR 20130601-20220617/UP) AND 2013-2022/PY L13 437 SEA (L12/HUMAN OR (L12 NOT ANIMALS/CT)) NOT REVIEW/DT AND ARTICLE/DT L14 555615 SEA KIDNEY DISEASES+NT/CT L15 584483 SEA (NEPH? OR KIDNEY OR RENAL OR URE? OR URI? OR URO? OR GLOMERULAR?)(2A)(DISORDER? OR DISEASE? OR FAILURE? OR DYSFUNCTION? OR INSUFFICIEN? OR SYMPTOM? OR SYNDROM? OR DAMAGE? OR DISTURBAN? OR IMPAIR?) OR NEPHROPATH? L16 96 SEA L13 AND (L14 OR L15) L17 34402 SEA KIDNEY DISEASES+NT/CT(L)CI/CT L18 75 SEA L16 NOT L17 SET NOTICE DISPLAY LOGIN

	SET NOTICE SEARCH LOGIN D L18 ALL 1-75"

Appendix 5

Search conditions for public literature

Appendix 5-1 Patients with sepsis

Ichushi	#1 Hydroxyethyl/AL and (デンプン/TH or Starch/AL) and Derivatives/TH or "HES 130-0.4"/TH or ボルベン/al or VOLUVEN/al or サリンヘス /al or ヘスパンダー/al or Salinhes/al or Hespan/al or Hydroxyethylstarch/al or Hydroxyethyl-starch/al or "Hydroxyethyl starch"/al or ヒドロキ シエチルスターチ/al or ヒドロキシエチル澱粉/al or "HES 130"/al or HES-130/al or HES130/al or "HES 70"/al or HES-70/al or HES70/al #2 #1 and (pt=症例報告 or pt=症例検討会 or 症例報告/ta or "case report"/ta) #3 (#2) and (PDAT=2013/6/1:2022/6/17 or IDAT=2013/6/1:2022/6/17) and (DT=2013:2022) #4 ((#3 and (CK=ヒト or ヒト/TH or 人間/TH)) or (#3 not (CK=動物 or 動物/TH))) and (PT=原著論文,会議録,症例検討会) #5 敗血症/TH or 敗血症/AL or 敗血病/AL or 敗血性疾患/AL or 菌血症/AL or セプシス/AL or Sepsis/AL or Septic/AL or Sapremia/AL or septicemia/AL or ゼプシス/AL or bacteremia/al #6 #4 and #5

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp

Appendix 5-2 Critically ill patients

Ichushi	#1 Hydroxyethyl/AL and (デンプン/TH or Starch/AL) and Derivatives/TH or "HES 130-0.4"/TH or ボルベン/al or VOLUVEN/al or サリンヘス/al or ヘスパンダー/al or Salinhes/al or Hespan/al or Hydroxyethylstarch/al or Hydroxyethyl-starch/al or "Hydroxyethyl starch"/al or ヒドロキシエチルスターチ/al or ヒドロキシエチル澱粉/al or "HES 130"/al or HES-130/al or HES130/al or "HES 70"/al or HES-70/al or HES70/al #2 #1 and (pt=症例報告 or pt=症例検討会 or 症例報告/ta or "case report"/ta) #3 (#2) and (PDAT=2013/6/1:2022/6/17 or IDAT=2013/6/1:2022/6/17) and (DT=2013:2022) #4 ((#3 and (CK=ヒト or ヒト/TH or 人間/TH)) or (#3 not (CK=動物 or 動物/TH))) and (PT=原著論文,会議録,症例検討会) #5 (重症/al not 重症度/al) or 重度/al or 重篤/al or severe/al or life-threaten/al or "life threaten"/al or "critically ill"/al or critically-ill/al #6 #4 and #5

Appendix 5-3 Patients with severe hepatic impairment

Ichushi	#1 Hydroxyethyl/AL and (デンプン/TH or Starch/AL) and Derivatives/TH or "HES 130-0.4"/TH or ボルベン/al or VOLUVEN/al or サリンヘス/al or ヘスパンダー/al or Salinhes/al or Hespan/al or Hydroxyethylstarch/al or Hydroxyethyl-starch/al or "Hydroxyethyl starch"/al or ヒドロキシエチルスターチ/al or ヒドロキシエチル澱粉/al or "HES 130"/al or HES-130/al or HES130/al or "HES 70"/al or HES-70/al or HES70/al #2 #1 and (pt=症例報告 or pt=症例検討会 or 症例報告/ta or "case report"/ta) #3 (#2) and (PDAT=2013/6/1:2022/6/17 or IDAT=2013/6/1:2022/6/17) and (DT=2013:2022) #4 ((#3 and (CK=ヒト or ヒト/TH or 人間/TH)) or (#3 not (CK=動物 or 動物/TH))) and (PT=原著論文,会議録,症例検討会) #5 肝臓疾患/TH or 肝疾患/AL or 肝障害/AL or 肝機能障害/AL or 肝腫瘤性疾患/AL or 肝臓疾患/AL or 肝臓病/AL or 肝病変/AL or 肝分葉異常/AL or 肝葉萎縮/AL or 障害肝/AL or 肝右葉低形成/AL or 肝機能低下/AL or 肝臓機能低下/AL or 肝臓機能障害/AL or 肝臓障害/AL or 肝機能異常/AL or 肝傷害/AL or 肝臓傷害/AL or 肝機能傷害/AL or 肝臓機能傷害/AL or "liver DISEASE"/al or "liver Disorder"/al or "liver failure"/al or "liver dysfunction"/al or "liver insufficien"/al #6 #4 and #5

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Appendix 5-4 Patients with severe coagulation disorder

Ichushi	#1 Hydroxyethyl/AL and (デンプン/TH or Starch/AL) and Derivatives/TH or "HES 130-0.4"/TH or ボルベン/al or VOLUVEN/al or サリンヘス/al or ヘスパンダー/al or Salinhes/al or Hespan/al or Hydroxyethylstarch/al or Hydroxyethyl-starch/al or "Hydroxyethyl starch"/al or ヒドロキシエチルスターチ/al or ヒドロキシエチル澱粉/al or "HES 130"/al or HES-130/al or HES130/al or "HES 70"/al or HES-70/al or HES70/al #2 #1 and (pt=症例報告 or pt=症例検討会 or 症例報告/ta or "case report"/ta) #3 (#2) and (PDAT=2013/6/1:2022/6/17 or IDAT=2013/6/1:2022/6/17) and (DT=2013:2022) #4 ((#3 and (CK=ヒト or ヒト/TH or 人間/TH)) or (#3 not (CK=動物 or 動物/TH))) and (PT=原著論文,会議録,症例検討会) #5 血液凝固異常/TH or 凝固障害/al or 凝固因子障害/al or 凝固異常/al or 凝固因子異常/al or "Blood Coagulation Disorder"/al or "Blood Coagulation Factor Disorder"/AL or Coagulopathy/al #6 #4 and #5

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp

Appendix 5-5 Patients with thermal burn

Ichushi	#1 Hydroxyethyl/AL and (デンプン/TH or Starch/AL) and Derivatives/TH or "HES 130-0.4"/TH or ボルベン/al or VOLUVEN/al or サリンヘス/al or ヘスパンダー/al or Salinhes/al or Hespan/al or Hydroxyethylstarch/al or Hydroxyethyl-starch/al or "Hydroxyethyl starch"/al or ヒドロキシエチルスターチ/al or ヒドロキシエチル澱粉/al or "HES 130"/al or HES-130/al or HES130/al or "HES 70"/al or HES-70/al or HES70/al #2 #1 and (pt=症例報告 or pt=症例検討会 or 症例報告/ta or "case report"/ta) #3 (#2) and (PDAT=2013/6/1:2022/6/17 or IDAT=2013/6/1:2022/6/17) and (DT=2013:2022) #4 ((#3 and (CK=ヒト or ヒト/TH or 人間/TH)) or (#3 not (CK=動物 or 動物/TH))) and (PT=原著論文,会議録,症例検討会) #5 熱傷/TH or 熱傷/AL or やけど/AL or 温熱性外傷/AL or 温熱性損傷/AL or 熱損傷/AL or 熱焼創/AL or BURN/ta #6 #4 and #5

Appendix 5-6 Patients with dehydration

Ichushi	#1 Hydroxyethyl/AL and (デンプン/TH or Starch/AL) and Derivatives/TH or "HES 130-0.4"/TH or ボルベン/al or VOLUVEN/al or サリンヘス/al or ヘスパンダー/al or Salinhes/al or Hespan/al or Hydroxyethylstarch/al or Hydroxyethyl-starch/al or "Hydroxyethyl starch"/al or ヒドロキシエチルスターチ/al or ヒドロキシエチル澱粉/al or "HES 130"/al or HES-130/al or HES130/al or "HES 70"/al or HES-70/al or HES70/al #2 #1 and (pt=症例報告 or pt=症例検討会 or 症例報告/ta or "case report"/ta) #3 (#2) and (PDAT=2013/6/1:2022/6/17 or IDAT=2013/6/1:2022/6/17) and (DT=2013:2022) #4 ((#3 and (CK=ヒト or ヒト/TH or 人間/TH)) or (#3 not (CK=動物 or 動物/TH))) and (PT=原著論文,会議録,症例検討会) #5 脱水症/TH or 脱水/AL or 水欠症/AL or DEHYDRAT/al or Anhydrat/al #6 #4 and #5

Appendix 5-7 Organ transplant patients

Ichushi	#1 Hydroxyethyl/AL and (デンプン/TH or Starch/AL) and Derivatives/TH or "HES 130-0.4"/TH or ボルベン/al or VOLUVEN/al or サリンヘス/al or ヘスパンダー/al or Salinhes/al or Hespan/al or Hydroxyethylstarch/al or Hydroxyethyl-starch/al or "Hydroxyethyl starch"/al or ヒドロキシエチルスターチ/al or ヒドロキシエチル澱粉/al or "HES 130"/al or HES-130/al or HES130/al or "HES 70"/al or HES-70/al or HES70/al #2 #1 and (pt=症例報告 or pt=症例検討会 or 症例報告/ta or "case report"/ta) #3 (#2) and (PDAT=2013/6/1:2022/6/17 or IDAT=2013/6/1:2022/6/17) and (DT=2013:2022) #4 ((#3 and (CK=ヒト or ヒト/TH or 人間/TH)) or (#3 not (CK=動物 or 動物/TH))) and (PT=原著論文,会議録,症例検討会) #5 臓器移植/TH or 臓器保存/TH or 臓器移植/al or 臓器グラフト/al or 腎移植/al or 肺移植/al or (心臓移植/TH or 心移植/AL) or (肝臓移植/TH or 肝移植/AL) or 腸移植/al or 膵移植/al or 腎臓移植/al or 心臓移植/al or 肝臓移植/al or 膵臓移植/al or 移植腎/al or 移植肺/al or 移植心/al or 移植肝/al or 移植腸/al or 移植膵/al or 腎グラフト/al or 肺グラフト/al or 心グラフト/al or 肝グラフト/al or 腸グラフト/al or 膵グラフト/al or ("移植片"/TH or "organ transplant"/AL) or "organ graft"/al or "renal transplant"/al or "kidney transplant"/al or "renal graft"/al or "kidney graft"/al or "lung transplant"/al or "pulmonary transplant"/al or "lung graft"/al or "pulmonary graft"/al or "cardiac transplant"/al or "heart transplant"/al or "cardiac graft"/al or "heart graft"/al or "liver transplant"/al or "liver graft"/al or "hepatic transplant"/al or "hepatic graft"/al or "bowel transplant"/al or "pancreas transplant"/al or "pancreas graft"/al #6 #4 and #5

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Appendix 5-8 Patients with renal failure

Ichushi	#1 Hydroxyethyl/AL and (デンプン/TH or Starch/AL) and Derivatives/TH or "HES 130-0.4"/TH or ボルベン/al or VOLUVEN/al or サリンヘス/al or ヘスパンダー/al or Salinhes/al or Hespan/al or Hydroxyethylstarch/al or Hydroxyethyl-starch/al or "Hydroxyethyl starch"/al or ヒドロキシエチルスターチ/al or ヒドロキシエチル澱粉/al or "HES 130"/al or HES-130/al or HES130/al or "HES 70"/al or HES-70/al or HES70/al #2 #1 and (pt=症例報告 or pt=症例検討会 or 症例報告/ta or "case report"/ta) #3 (#2) and (PDAT=2013/6/1:2022/6/17 or IDAT=2013/6/1:2022/6/17) and (DT=2013:2022) #4 ((#3 and (CK=ヒト or ヒト/TH or 人間/TH)) or (#3 not (CK=動物 or 動物/TH))) and (PT=原著論文,会議録,症例検討会) #5 腎臓疾患/TH or 腎臓疾患/al or 腎機能異常/al or ネフロパシー/AL or 腎機能障害/AL or 腎機能疾患/AL or 腎機能低下/AL or 腎疾患/AL or 腎症/AL or 腎障害/AL or 腎臓病/AL or 腎病変/AL or 腎瘻/AL or 腎ろう/AL or 腎不全/AL or 腎機能高度低下/AL or "KIDNEY DISEASE"/al or "KIDNEY Disorder"/al or "KIDNEY failure"/al or "KIDNEY dysfunction"/al or "KIDNEY insufficien"/al or "renal DISEASE"/al or "renal Disorder"/al or "renal failure"/al or "renal dysfunction"/al or "renal insufficien"/al #6 #4 and #5 #7 #6 not 腎臓疾患;化学的誘発/Th

Appendix 6

[Hydroxyethylated starch 130000]

Revision in line with the Instructions for Package Inserts of Prescription Drugs, PAB Notification No. 606 by the Director General of Pharmaceutical Affairs Bureau, MHW, dated April 25, 1997 (Old instructions): Revised language is underlined.

Current	Revision
Warnings The condition of patients may be exacerbated when this drug is used in relative decreased blood volume during the management of critically ill patients <u>including patients with severe sepsis</u>. This drug should be administered only if the therapeutic benefits outweigh the risks. (See "11. Other Precautions.")	Warnings The condition of patients may be exacerbated when this drug is used in relative decreased blood volume during the management of critically ill patients. This drug should be administered only if the therapeutic benefits outweigh the risks. (See "11. Other Precautions.")
Contraindications (This drug should not be administered to the following patients.) (1)-(6) (omitted) (N/A)	Contraindications (This drug should not be administered to the following patients.) (1)-(6) (omitted) <u>(7) Patients with sepsis [The condition of patients may be exacerbated.] (See "11. Other Precautions.")</u>
Precautions	Precautions

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11. Other Precautions (1) In overseas clinical studies, it has been reported that the use of HES preparations in patients with severe sepsis was associated with a higher mortality risk at 90 days after administration and a higher percentage of patients requiring renal replacement therapy, as compared with the use of acetated Ringer's solution. It has been also reported that the use of HES preparations in patients admitted to the ICU including patients with sepsis was associated with a higher percentage of patients requiring renal replacement therapy, as compared with the use of saline, although the mortality risk up to 90 days after administration did not increase. (See "Warnings.") (2) (omitted)	11. Other Precautions (1) In overseas clinical studies, it has been reported that the use of HES preparations in patients with severe sepsis was associated with a higher mortality risk at 90 days after administration and a higher percentage of patients requiring renal replacement therapy, as compared with the use of acetated Ringer's solution. It has been also reported that the use of HES preparations in patients admitted to the ICU including patients with sepsis was associated with a higher percentage of patients requiring renal replacement therapy, as compared with the use of saline, although the mortality risk up to 90 days after administration did not increase. (See "Warnings," "Contraindications.") (2) (omitted)

N/A: Not Applicable. No corresponding language is included in the current Precautions.

[Hydroxyethylated starch 130000]

Revision in line with the Instructions for Electronic Package Inserts of Prescription Drugs, etc. PSEHB Notification No. 0611-1 by the Director of Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated June 11, 2021 (New instructions): Revised language is underlined.

Current	Revision
1. WARNINGS The condition of patients may be exacerbated when this drug is used in relative decreased blood volume during the management of critically ill patients <u>including patients with severe sepsis</u>. This drug should be administered only if the therapeutic benefits outweigh the risks. [See 15.1.1.]	1. WARNINGS The condition of patients may be exacerbated when this drug is used in relative decreased blood volume during the management of critically ill patients. This drug should be administered only if the therapeutic benefits outweigh the risks. [See 15.1.1.]
2. CONTRAINDICATIONS (This drug should not be administered to the following patients.) 2.1-2.6 (omitted) (N/A)	2. CONTRAINDICATIONS (This drug should not be administered to the following patients.) 2.1-2.6 (omitted) <u>2.7 Patients with sepsis [The condition of patients may be exacerbated.] [See 15.1.1.]</u>
15. OTHER PRECAUTIONS 15.1 Information Based on Clinical Uses	15. OTHER PRECAUTIONS 15.1 Information Based on Clinical Uses

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15.1.1 In overseas clinical studies, it has been reported that the use of HES preparations in patients with severe sepsis was associated with a higher mortality risk at 90 days after administration and a higher percentage of patients requiring renal replacement therapy, as compared with the use of acetated Ringer's solution. It has been also reported that the use of HES preparations in patients admitted to the ICU including patients with sepsis was associated with a higher percentage of patients requiring renal replacement therapy, as compared with the use of saline, although the mortality risk up to 90 days after administration did not increase. [See 1.]	15.1.1 In overseas clinical studies, it has been reported that the use of HES preparations in patients with severe sepsis was associated with a higher mortality risk at 90 days after administration and a higher percentage of patients requiring renal replacement therapy, as compared with the use of acetated Ringer's solution. It has been also reported that the use of HES preparations in patients admitted to the ICU including patients with sepsis was associated with a higher percentage of patients requiring renal replacement therapy, as compared with the use of saline, although the mortality risk up to 90 days after administration did not increase. [See 1, 2.7.]
15.1.2 (omitted)	15.1.2 (omitted)

N/A: Not Applicable. No corresponding language is included in the current Precautions.

[Hydroxyethylated starch 70000/sodium chloride/potassium chloride/calcium chloride hydrate/sodium lactate, hydroxyethylated starch 70000]

Revision in line with the Instructions for Package Inserts of Prescription Drugs, PAB Notification No. 606 by the Director General of Pharmaceutical Affairs Bureau, MHW, dated April 25, 1997 (Old instructions): Revised language is underlined.

Current	Revision
Contraindications (This drug should not be administered to the following patients.) (1)-(3) (omitted) (N/A)	Contraindications (This drug should not be administered to the following patients.) (1)-(3) (omitted) (4) Patients with sepsis [The condition of patients may be exacerbated.] (See "7. Other Precautions.")
Precautions Concerning Indications This drug should not be used for relative decreased blood volume during the management of critically ill patients including patients with severe sepsis. (See "7. Other Precautions.")	Precautions Concerning Indications This drug should not be used for relative decreased blood volume during the management of critically ill patients. (See “7. Other Precautions.”)
Precautions 7. Other Precautions (1) (omitted) In overseas clinical studies, it has been reported that the use of	Precautions 7. Other Precautions (1) (omitted) In overseas clinical studies, it has been reported that the use of

HES preparations in patients with severe sepsis was associated with a higher mortality risk at 90 days after administration and a higher percentage of patients requiring renal replacement therapy, as compared with the use of acetated Ringer's solution. It has been also reported that the use of HES preparations in patients admitted to the ICU including patients with sepsis was associated with a higher percentage of patients requiring renal replacement therapy, as compared with the use of saline, although the mortality risk up to 90 days after administration did not increase. (See "Precautions Concerning Indications.")	HES preparations in patients with severe sepsis was associated with a higher mortality risk at 90 days after administration and a higher percentage of patients requiring renal replacement therapy, as compared with the use of acetated Ringer's solution. It has been also reported that the use of HES preparations in patients admitted to the ICU including patients with sepsis was associated with a higher percentage of patients requiring renal replacement therapy, as compared with the use of saline, although the mortality risk up to 90 days after administration did not increase. (See "Contraindications," "Precautions Concerning Indications.")
(3) (omitted)	(3) (omitted)

N/A: Not Applicable. No corresponding language is included in the current Precautions.