The clinical trial information provided in this public disclosure synopsis is supplied for informational purposes only.

Please note that the results reported in any single trial may not reflect the overall potential risks or benefits of a product which are based on an evaluation of an entire research program.

Before prescribing any Takeda products, healthcare professionals should consult prescribing information for the product approved in their country.

Clinical Trial Report Synopsis

Name of Company: Nycomed	**Tabular format** Referring to Part of the Dossier:	*(For National Authority Use only)*
Name of Finished Product: TachoSil®		
Name of Active Ingredient: Fibrinogen (human) and thrombin (human)		
Title of Trial: A prospective, multi-centre, phase III-b study of TachoSil® in paediatric patients scheduled for resection of the liver with or without segmental liver transplantation		
Principal Investigators (in alphabetical order): [redacted]		
Trial Centre(s): Two centres in UK		
Publication (reference): None		
Studied period (years): May 2006 – July 2007	**Phase of development:** Therapeutic confirmatory	
Objectives: To collect data on efficacy, i.e. intra-operative haemostasis, and safety of TachoSil as treatment to control local bleeding in children undergoing surgical resection of the liver with or without segmental transplantation. The study was part of a post-authorisation commitment required by CHMP as all previous trials were in adults.		
Methodology: Open, prospective, non-comparative		
Number of patients (total and for each treatment): Planned: 40. Study put on halt and abandoned after enrolment of 16 as it proved very difficult to conduct a study in this population of severely ill children within the strict boundaries of GCP (a.o delayed availability of hospital records and the complexities of multidisciplinary critical care).		
Diagnosis and main criteria for inclusion: Main inclusion criteria: at least segmental resection of the liver or resection followed by placement of a segmental liver graft; age: above 4 weeks and below 6 years; minor or moderate haemorrhage after primary surgical haemostatic procedures of major vessels. Exclusion criteria: several		

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Test product, dose and mode of administration, batch number:

Tachosil (equine collagen sponge with human fibrinogen and thrombin); number of sponges as needed applied to the cut surface of the liver. Batch no.:

Duration of treatment:

Intra-operative application with 6 months follow-up

Reference therapy, dose and mode of administration, batch number:

Not applicable

Criteria for evaluation:

Efficacy:

Time to intra-operative haemostasis after the application of TachoSil

Safety

Adverse events

Statistical methods:

No statistical testing was performed; results presented on the basis of descriptive statistics

SUMMARY:

The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice and after approval by the relevant Ethics Committees and Competent Authorities; signed informed consent was obtained from the parent(s)/legal guardian for all children

No study-specific procedures were performed except the use of TachoSil, assessment of time to haemostasis and 6-month follow-up. As these severely ill children spent most of their time in intensive care units at the hospitals strictly adherence to GCP (monitoring) was very difficult resulting a.o. in late reporting of AEs and SAEs. Due to this the sponsor had the study put on halt and a thorough investigation focusing on the reporting of AEs/SAEs was initiated. No safety concerns were raised, but at a meeting with the CHMP Rapporteur it was agreed to discontinue the study a.o. because most information collected is rather related to the underlying serious disease than the use of TachoSil.

Sixteen children were enrolled in the study before it was discontinued, three had segmental liver resection and 13 resection followed by transplantation of a graft. Two discontinued during the study – one died from multi organ failure and the other one needed a re-transplantation after 4 months. In- and exclusion criteria were violated by three children, one both by being too old and having liver combined with kidney transplantation, one by being re-transplanted and one by having combined liver and kidney transplantation.

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Seven of the 16 children were male, median (range) age was 15 (2.5 – 147.5) months and BMI 17.4 (13.8 – 22.0) kg/m2.

Efficacy results

Thirteen – 81.3% (95% CI: 61.8 – 100%) – obtained haemostasis at 3 minutes , one after 8 minutes and two failed on TachoSil and other haemostatic remedies had to be used.

Safety results

A total of 64 adverse events were reported in 14 children. Further to these events information about post-operative infections (29 events), re-operations (9 events) and graft rejections (6 events) were collected so in total 108 events were reported.

Six events in five children were classified as serious and among these one died from overwhelming sepsis leading to multi organ failure.

None of the events reported were considered possible or probable related to the use of TachoSil.

CONCLUSION:

The study showed TachoSil to be effective in obtaining intra-operative haemostasis in the majority of children undergoing liver resection with or without segmental liver transplantation. Furthermore it was concluded from the safety data collected that TachoSil was not considered to be related to any of the AE/SAEs reported and has demonstrated an acceptable safety profile and is thus clinically appropriate for use in this population.

Date: 21. May 2008