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Product name: TachoSil
Procedure number: H-505-II-06

SCIENTIFIC DISCUSSION

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I. SCIENTIFIC DISCUSSION

1.1. Introduction

The applicant has performed a clinical trial (study TC-015-IN) in patients undergoing surgical treatment for surgical resection of superficial renal tumour. This is part of a follow up measure, which was asked to the MAH.

Based on these efficacy and safety data, the MAH proposes to amend the indication section and to use the product for any types of surgery; mainly to delete the sentence "Efficacy has only been demonstrated in liver surgery" in section 4.1, and to implement a short advice on the additional study in renal surgery in section 5.1. Pharmacodynamics properties.
In addition, an update of section 4.8 undesirable events to introduce pyrexia as an undesirable event and minor update of local representative is proposed.

1.2 Clinical aspects

Since the initial application, Tachosil has been approved for the following indication with the restrictions mentioned below.

- TachoSil is indicated for supportive treatment in surgery for improvement of haemostasis where standard techniques are insufficient.

Specific data have not been obtained on the use of this product in neurosurgery, in vascular surgery or in gastrointestinal anastomoses.
Furthermore, the use of TachoSil for tissue sealing is not supported based on the results of the clinical studies undertaken.

Indeed, at time of first application, the MAH submitted data in liver and lung surgery. During lung surgery the product's qualities in the indication of "tissue sealing" were tested and did not show sufficient efficacy. Therefore, the use of Tachosil is not considered in this type of indication.

1.2.1-Methodology- study design

Study TC-015-IN:
This study was an open, randomised, prospective, multi-centre, parallel-group trial comparing the efficacy and safety of TachoSil with those of standard surgical treatment in patients undergoing surgical resection of superficial renal tumour.

The trial population consisted of patients undergoing nephron-sparing resection of superficial renal tumours. Patients were eligible for inclusion in the trial if the tumour was not infiltrating the urinary tract, and if the surgical intervention did not require major kidney resection or extirpation, and if the patient was scheduled for open surgery.
After primary haemostasis the patients were randomised to TachoSil or standard suturing.

One hundred and eighty five patients were included in the study.

The primary objective was to test haemostatic efficacy and safety of TachoSil by comparison of two trial treatments, TachoSil and standard suturing.
The primary efficacy variable was the intra-operative time to haemostasis as well as the proportion of subjects with haemostasis after 10 min of trial treatment. The surrogate endpoint, occurrence of haematoma on Day 2 after surgery, was also used for comparison of haemostatic efficacy.

The secondary objectives included description of volume and haemoglobin concentration of post-operative drainage fluid as well as surgeon's rating of usefulness of trial treatment and occurrence of haematoma on Day 2 after surgery. Safety was evaluated by occurrence of adverse events.

1.2.2- Efficacy results

The primary efficacy endpoints, i.e. time to haemostasis and proportion of subjects with haemostasis after 10 min of trial treatment, showed a statistically significant difference in favour of TachoSil.

Time to haemostasis:

	TachoSil	Standard
Average (median) time, min	5.3 (3.0)	9.5 (8.0)

The difference between treatments was statistically significant p<0,0001 (log-rank test)

Proportion of subjects with haemostasis at 10 min:

	TachoSil	Standard
Before/at 10 min	84 (92%)	62 (67%)
After 10 min	7 (8%)	30 (33%)

p<0.0001 (Cochran-Mantel-Haenszel)

The secondary endpoints of haematoma formation, average volume of drainage fluid on day 1, average duration of drainage, Hb concentration of drainage fluid on day 1, blood and liquid substitution on days 1 and 2 after surgery, and usefulness of trial treatment rated by surgeon, did not reveal any difference between the groups.

The study results clearly show favourable haemostatic efficacy for Tachosil for the primary efficacy variable compared to standard treatment following secondary haemostasis in renal surgery.

1.2.3- Safety results

A total of 163 adverse events were reported during the trial period: 99 events in 43 TachoSil subjects and 64 events in 37 standard treatment subjects. The total number of adverse events and the number of serious adverse events were higher in TachoSil subjects, which seems incidental as all individual adverse events were equally distributed except fever and extravasation of urine, both common types of events in renal surgery.

Fever (coded as pyrexia, postoperative fever and body temperature increased) was reported in 17 TachoSil subjects and in 7 standard treatment subjects. All subjects had several risk factors for development of fever, e.g. recent surgery, general anaesthesia and cancer.
Extravasation of urine was reported in three TachoSil subjects (3.3%) and in no standard treatment subject. Two of the events were serious and considered unlikely related to TachoSil by Investigators. No subject withdrew from the trial due to adverse events.

It is proposed to add pyrexia in section 4.8 undesirable event as it clarifies the condition of fever as a general possibility and not only under immunological aspects. The sentence will be as follows
under the system organ class general disorder and administration site condition :
"Pyrexia may occur commonly."

In addition, the package leaflet is updated accordingly to add fever as a potential adverse event:
You may experience fever when taking Tachosil.

1.3 Discussion

The results of this study are in accordance with previous experience with TachoSil trials in liver resection, where TachoSil shows significant shorter time to haemostasis compared to standard techniques combined with a sufficient safety profile.

The target population of the product still remains the same. During the procedure, Experts'opinionwere requested from the MAH on the question of extrapolation of results obtained in the treatment of bleeding episodes in high-level surgery (liver resection and superficial renal tumour extirpation) to surgery in general in various organs and tissues.
The conclusions of the experts clearly indicate that there is a scientific and practical surgical justification for the use of TachoSil as supportive haemostatic treatment in all organs, based on the clinical data obtained in the two different organ systems, liver and kidney. Furthermore, liver surgery and renal surgery are challenging bleeding situations and the product would be expected to work in less severe bleeding situations.

Consistency in results of all studies even with different comparators confirms that treatment effects of TachoSil are not organ specific. In fact, it appears that except for specific areas of application, e.g. vascular surgery, GI-anastomoses and neurosurgery (which require specific data as described in the SPC section 4.4), TachoSil can be regarded by the surgeon as a general product for improvement of secondary haemostasis.

In addition, from the predecessor products TachoComb and TachoComb H, which both differ from TachoSil in containing aprotinin and TachoComb bovine thrombin, there are several years of experiences in a wide range of organs and surgical procedures i.e. urology abdominal-, neuro-, vascular-, heart and thoracic surgery, ENT and gynaecology.

The current indication for TachoSil represents a full indication as supportive treatment in surgery for improvement of haemostasis where standard techniques are insufficient. The sentence regarding liver surgery does not represent a restriction of the indication but provides information on where efficacy has been demonstrated.
Therefore, the data provided by the MAH could be extrapolated to other types of surgery, with the following restrictions:
The product is not intended for use in tissue sealing (such as lung surgery), vascular surgery, gastrointestinal anastomoses, neurosurgery as mentioned in the Tachosil SPC in accordance with the current core SPC on fibrin sealant/haemostatic products (CHMP/BPWG/153/00, July 2004). Additional specific studies would be required for granting these indications.

The CHMP is of the opinion that the data provided by the MAH (renal surgery study) do not represent an extension of indication as such but represent more a second proof of evidence of the efficacy in a second type of surgery.

Thus, it can be applied in most surgical situations with a predictable clinical outcome, which is correctly reflected in the SPC with the proposed changes. Therefore the deletion of the statement "Efficacy has only been demonstrated in livery surgery" in section 4.1 has adequately been justified.

In conclusion, based on the review of the data on the clinical study report TC-015-IN, regarding the use of Tachosil in renal surgery, the CHMP considers that the variation application EMEA/H/C/505/II/06 for TachoSil in the treatment of: "Supportive treatment in surgery for improvement of haemostasis where standard techniques are insufficient. (Efficacy has only been demonstrated in livery surgery)", is approvable for the proposed SPC and PIL changes:

SPC - Section 4.1:Therapeutic indications
Deletion of the sentence "*Efficacy has only been demonstrated in livery surgery"* in the indication section.

SPC: Undesirable events
Addition of pyrexia in the list of adverse events:
"Pyrexia may occur commonly."

SPC – Section 5.1 Pharmacodynamic properties
In order to update and more accurately reflect the study data, the information regarding the renal study is added as follows in section 5.1 of the SPC:
"Clinical studies demonstrating haemostasis were conducted in a total of 240 patients undergoing partial liver resection *and 185 patients undergoing surgical resection of superficial renal tumour*."

In addition, the PIL is updated to add fever as a possible adverse event and the applicant proposes an update of local representative in the patient leaflet.

II. CONCLUSION

On 26 January 2006 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.