Public assessment report for biological medicinal product
Afstyla® (Lonoctocog alfa)
31st July 2019, Division of Health Product Enterprise Services,
Thai Food and Drug Administration

Name of product	Lonoctocog alfa, Afstyla®
Active Substance(s) **(ATC code)**	INN: Lonoctocog alfa (B02BD)
Pharmaceutical form	Powder and solvent for solution for injection
Strength	250 IU/vial, 500 IU/vial, 1000 IU/vial, 2000 IU/vial, 3000 IU/vial
Route(s) of administration	Intravenous use
Therapeutic indication(s)	**Indication as stated in SmPC:** Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). **Indications as stated in the patient information leaflet (PIL):** ใช้รักษาและป้องกันภาวะเลือดออกในผู้ป่วยโรคฮีโมฟีเลีย เอ
Submitted number and date of submission	1C 15001/62 (NB) 11 October 2018
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Part 1: Introduction and summary review

Hemophilia A, also called factor VIII (FVIII) deficiency or classic hemophilia, is a genetic disorder caused by missing or defective factor VIII, a clotting protein. Hemophilia A is an X-linked, recessive disorder caused by deficiency of functional plasma clotting factor VIII (FVIII), which may be inherited or arise from spontaneous mutation.

People with hemophilia A often bleed longer than other people. Bleeds can occur internally, into joints and muscles, or externally, from minor cuts, dental procedures or trauma. How frequently a person bleeds and the severity of those bleeds depends on how much FVIII is in the plasma, the straw-colored fluid portion of blood[1].

Normal plasma levels of FVIII range from 50% to 150%. Levels below 50%, or half of what is needed to form a clot, determine a person's symptoms. In severe hemophilia A patient, less than 1% of FVIII in the blood, experience bleeding following an injury and may have frequent spontaneous bleeding episodes, often into their joints and muscles.

Guideline for the management of hemophilia of World Federation of hemophilia recommend prophylaxis of bleeding is gold therapy for destroyed joint prevention that lead to be disability[2]. Guideline for the management of hemophilia of Thailand classified in treatment on demand, early treatment and prophylaxis treatment. Factor VIII replacement is the first-choice treatment[3].

Afstyla is formulated as a sterile, non-pyrogenic, preservative-free, lyophilized, white to slightly yellow powder or friable mass intended for intravenous administration provided in a single-use vial. It is a single-chain recombinant Factor VIII produced in Chinese hamster ovary (CHO) cells. It is a construct where the B-domain occurring in wild type full-length Factor VIII has been truncated and 4 amino acids of the adjacent acidic a3 domain were removed (amino acids 765 to 1652 of full-length Factor VIII). AFSTYLA is expressed as a single-chain Factor VIII molecule with covalent linkage between heavy and light chains; thereby keeping the molecule in the single chain form resulting in increased stability and increased von Willebrand Factor (VWF) affinity. Several studies were conducted comparing pharmacokinetics profile with marketed full-length rFVIII such as Advate.

Afstyla has demonstrated a higher VWF affinity relative to full-length rFVIII. VWF stabilizes factor VIII and protects it from degradation. Activated Afstyla has an amino acid sequence identical to endogenous FVIIIa.

The pharmacodynamic activity of Afstyla did not differ significantly from the marketed Advate and the overall hemodynamic capacity of Afstyla appears to be comparable to Advate when dosed according to chromogenic FVIII activity and the overall PK properties in Cynomolgus monkeys were comparable to Advate.

The pharmacokinenic study in clinical study of Afstyla revealed slightly higher half-life and AUC values whereas the clearance was somewhat reduced in comparison to Advate but these differences are not considered clinically relevant, Pharmacokinetic of Afstyla and Advate are comparable.

In conclusion, Pharmacodynamic activity and pharmacokinetic properties Afstyla shows comparable as marketed rFVIII products such as Advate.

Part 2: Summary of the dossier

2.1 Type of marketing authorization application

Product type: New biological medicine

Application type: Stand-alone application(including quality, non-clinic and clinic)

Review method: Abbreviated assessment ; un-redacted evaluation report from EMA

2.2 Administrative data

2.2.1 Product

Name of Product: Invented name	Afstyla®
Active Substance(s)	Lonoctocog alpha
Strength	Lonoctocog alpha powder and solvent for solution for injection 250 IU, 500 IU, 1000 IU, 2000 IU, 3000 IU
Therapeutic class **(ATC Code)**	Blood coagulation factors (B02BD)
Pharmaceutical form	Powder and solvent for solution for injection
Route of administration	Intravenous use
Drug Characteristics	White or slightly yellow powder or friable mass and clear, colorless solvent for solution for injection
Packaging	Colorless, neutral glass vial Type I, and a bromobutyl rubber stopper with an aluminum overseal closure. The over seals are color coded based on presentation size as follows: - 250 IU green striped / orange - 500 IU green striped / blue - 1000 IU green striped / green

	- 1500 IU green striped / turquoise - 2000 IU green striped / purple - 2500 IU green striped / light grey - 3000 IU green striped / yellow
Package size(s)	Each box contains 1) Lyophilized powder in glass vial type I ; The 250, 500, and 1000 IU which are all filled in vials of 6 mL, The 2000 and 3000 IU fill sizes use a 10 mL vial 2) Sterile water for injection in cleaned, depyrogenised and sterilized infusion vials of tubular, colorless glass ; 5 ml or 2.5 ml depend on size 3) Filter transfer device 4) Venipuncture set 5) Syringe 6) Plaster 7) Swab

2.2.2 Source

- **Name and address of the applicant for importation**

Zuellig pharma Ltd, 2 Pleonjit center 8th - 9th Floor, Sukhumvit Rd, Klongtoey, Bangkok 10120, Thailand

- **Name and address of the manufacturer(s) of the dosage form**

CSL Behring GmbH , Emil-von-Behring-Strasse 76 Rd., Marburg, Germany

- Name and address of the packaging and the secondary packaging

The same as stated in the name and address of the manufacturer

- **Name and address of the manufacturer(s) which take responsibility on inspection before release**

The same as stated in the name and address of the manufacturer

Evaluation results

CSL Behring GmbH was licensed as manufacturer for modern medicine used in human. The manufacturer has been permitted both in sterile products, non-sterile products and biotechnology product. The manufacturer has been certified GMP compliance by National Institute of Pharmacy, Germany; membered of PIC/s.

Market authorization holder, Zuellig Pharma CO. LTD, also attached GMP clearance certificate approved by Bureau of drug control, Thai FDA. It performs manufacturer has standard manufacturing process which is equivalent standard control in Thailand.

Part 3: Analytical Physico-Chemical, Biological and Microbiological Documentation

3.1 Drug substance

3.1.1 General information

3.1.1.1 Nomenclature:

INN name: Lonoctocog alfa

The scientific name: Recombinant, single-chain coagulation factor VIII (rVIII-SingleChain)

3.1.1.2 Structure

Lonoctocog alfa is a single-chain recombinant Factor VIII construct where most of the B-domain occurring in wild-type, full-length FVIII and four amino acids of the adjacent acidic a3 domain were removed

3.1.1.2 Molecular weight

Lonoctocog alfa has amino acids in a single chain glycopeptide with a molecular weight of approximately 170 kDa.

3.1.2 Manufacture

3.1.2.1 Manufacturer(s)

The Manufacturer is in Germany, where has worked in manufacture and release testing of rVIII-SingleChain drug substance

3.1.2.2 Description of Manufacturing Process and Controls

The manufacturing steps from the starting material (working cell bank) to the drug substance which comprises 12 synthetic steps. These consist of an upstream cell culture process and downstream purification process.

Evaluation results

The manufacturer of Lonoctocog alfa has valid GMP certified by the competent authority of Germany. Manufacturing process and quality control is suitable by identification of critical steps in process and control including process validation, so all of documents confirm that drug substance manufacturing processes are reliable, suitable and acceptable.

3.1.4 Control of drug substance

Manufacturer defined specification of Lonoctocog alfa drug substance and analytical method.

Batch analysis

Data of lots including pilot scale batches and commercial scale batch show the results are met all of the specification criteria described in “Test and specifications”

Evaluation result

Specification, analytical method and validation method of drug substance were followed by European Pharmacopeia and in-house method was also evaluated by method validation on suitable parameters. In addition, manufacturer tested consistency on pilot and commercial batches the results shows all batches were consistency. Then all can summarized that manufacturing process, analytical method and process validation of drug substance was reliable, suitable and acceptable.

3.1.5 Container closure system

Drug substance can either be stored for short term in 20 L stainless steel vessels for immediate further processing, or in single-use gamma irradiation sterilized 6 L EVA bags for long-term storage at ≤ -65 °C. The bag manufacturer follows the applicable ISO and FDA regulations for medical devices. Design, manufacture and sterilization processes are conducted under conditions that reflect biopharmaceutical operations and meet cGMP requirements

Evaluation result

Drug substance contained in standard container is suitable, reliable and acceptable.

3.1.7 Stability

The active substance is either processed immediately after the virus filtration step or is stored in 6L EVA bags at ≤-65℃ for the claimed shelf-life of 36 months. Three lots were placed on stability for defined storage, time and temperature (≤ -65 °C for 36 months and ≤ 15 °C for 9 weeks).

The following parameters were tested covering purity, impurity profile, and structural and functional characteristics

Under accelerated and long term conditions, all tested parameters were within the specifications for the primary and supportive stability batches.

Evaluation results

Number of batch, condition, duration and parameters followed by ICH guideline are suitable. The stability results indicate that the active substance manufactured by the proposed suppliers sufficiently stable in the proposed container.

3.2 Drug product

3.2.1 Manufacture

The manufacturer of the drug product is CSL Behring GmbH, Germany. The GMP certificate issued by the competent authority of Germany.

The manufacturer of water for injections takes place at CSL Behring GmbH Emil von Behring Straße 76 35041 Marburg Germany.

Batch Formula

Description of manufacturing process and process control

The drug product manufacturing process consists of five main steps: formulation and sterile filtration, filling, lyophilization, capping and crimping, labeling and packaging. The flow diagram of the manufacturing process shows the steps and where the ingredients enter the process and where the in-process control tests are performed.

Evaluation result

CSL Behring GmbH is suitable and acceptable manufacturer of drug product and sterile water for injection. They show valid certificate of GMP compliance of a manufacturer from competent authority of Germany. The process is considered to be a standard manufacturing process. The in-process controls are adequate for controlling these steps. Major steps of the manufacturing process have been validated. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

3.2.2 Description and Composition of the drug product

The product is supplied as a single-use type I glass vials of 6 mL (250 IU, 500 IU, 1000 IU of lonoctocog alfa per vial) and 10 mL (1500 IU, 2000 IU, 2500 IU, 3000 IU of lonoctocog alfa per vial) intended for intravenous (i.v.) injection. The vials are closed with a rubber stopper and sealed with aluminum over seal closure using different colors for the various strengths.

Components	Quality Standard Reference*	Function
Powder vial		
rVIII-SingleChain	In-house	Active substance
L-Histidine	Ph. Eur., USP	Buffer
Polysorbate 80	Ph. Eur., NF	Stabilizer
Calcium Chloride	Ph. Eur., NF	Stabilizer
Sodium chloride	Ph. Eur., NF	Bulking agent, Stabilizer
Sucrose	Ph.Eur., NF	stabilizer

HCl	Ph.Eur.	pH adjustment
Solvent vial		
Water for injection	JP, Ph.Eur, USP	Dissolving agent

*Totally Standard reference was followed current version

Evaluation results

The formulation including active ingredient and excipients is complied with Ph.Eur and in-house specification that show formulation has standard and acceptable. Moreover they have no use novel excipients in the formulation.

3.2.3 Control of drug product

Drug product has quality control by specification, analytical method and validation method

Moreover, the quality controls of drug product and sterile water for injection have analytical method and validation method to assure their qualities in each lots.

Evaluation results

There are specification, analytical method and process validation. All of them conducted by acceptable standard. Manufacturing process of drug product and sterile water for injection followed Ph.Eur and in-house verified by analytical validation. Moreover, Manufacturer identify in process control in each steps for consistency. Overall we can summarise that manufacturing process of drug product and sterile water for injection are suitable, reliable, consistent and acceptable.

3.2.4 Container closure system

Description of packaging component of drug product is summarized as below :

Packaging	Description
Container	6 ml vial or 10 ml vial (Type 1 borosilicate glass per USP/Ph.Eur)
Closure	Bromobutyl rubber stopper (USP/Ph.Eur)
	Combination cap, Aluminium (Green Striped)/ polypropylene, Color depend on size.

Single-use colorless vials are used for rVIII-SingleChain lyophilized drug product. The containers are met the USP and Ph.Eur. requirements for parenteral administration.

The vials are closed with stoppers that comply with requirements of Ph. Eur. and current USP. The formulation of the stopper does not contain latex.

The stoppers are secured by combination caps consisting of an aluminum crimp cap and an integrated plastic disc. The crimp caps meet international standards.

The following packaging materials are used for water for injections filling sizes 2.5 ml and 5 ml, type I glass, colorless. They comply with Ph.Eur.

Evaluation result

Quality of container closure system of drug product and sterile water for injection comply with Ph.Eur., USP or international standard. MAH attached certificate of analysis data for considering, all results comply with the proposed specification. Then we can summarize that container closure of drug product is suitable and acceptable.

3.2.5 Stability

3.2.5.1 Drug product

The stability study was started to test the quality of the drug product under the following conditions.

Long term storage condition:

Scheduled Testing (months)	0	3	6	9	12	18	24	36
5°C ±3°C for 36 months	x	x	x	x	x	x	x	x
25°C ±2°C 60 % RH ±5 % RH for 3 months, afterwards 5°C ±3°C for 33 months	x	x	x	x	x	x	x	x

All specifications are met at the storage condition of 5°C for 36 months including storage at 25 °C for 3 months.

Accelerated condition, stress storage condition:

Scheduled Testing (months)	0	1	3	6	9	12
30°C ±2°C/75 % RH ±5 % RH for 12 months	x		x	x	x	x
40°C ±2°C/75 % RH ±5 % RH for 6 months	x	x	x	x		

Photo stability study

Photo stability study was performed according to ICH1B. The data from this study indicate that the drug product should be stored protected from the light.

3.2.5.2 Sterile water for injection stability

The shelf-life for the WFI filling size 2.5 ml and 5 ml is 60 months at 2-8°C . The studies supported comprising 2 study. All stability lots meet the specification of all parameters under all conditions applied.

3.2.5.3 After reconstitution stability

Type	Storage condition	Storage period	Sampling intervals
Stability after reconstitution after storage at 5°C	Storage at 20°C-25°C	36 months	0 and 36 month*
*** testing at the start, after 4 and 8 hours. Storage at 20°C-25°C**			

The reconstituted product was analyzed immediately after reconstitution, and 4 and 8 hours after reconstitution (storage at 20°C-25°C). All results are within the specification after reconstitution at the start of the study and after 36 months storage for all lots over 8 hours. However, drug product was tested at the start of the study and after 12, 24 and 36 months storage respectively. Chemical, physical and activity tests were performed immediately after reconstitution and 8, 24 and 48 hours after reconstitution (storage at 20-25) for all time intervals. All results were within the specifications.

Evaluation results

Stability test of drug product including number of batch, condition, duration and parameter is suitable. Drug product stability protocol conforms with ASEAN Guideline. So, the proposed shelf-life of 36 months in 2-8°C is acceptable.

Stability of sterile water for injection is 60 months in 2-8°C. then propose shelf-life of drug product is 36 months when keep in 2-8°C is acceptable.

After reconstitution the chemical and physical in-use stability has been demonstrated for 48 hours at room temperature (below 25 °C) is suitable and acceptable.

Assessor's conclusions on Quality

The overall assessment of EMA un-redacted assessment report as well as the evaluation according to ASEAN guidelines and relevant regulations can be summarized that the critical points relevant to efficacy and safety were satisfactory clarified. The assessment result was presented in the advisory expert meeting held on 31st July 2019. The expert panel concluded that overall quality data on manufacturing and quality control of drug substances and drug product are acceptable.

Part 4: Non-clinical documentation

4.1 Pharmacology

4.1.1 Primary pharmacodynamic studies

The pharmacodynamic activity of rVIII-SingleChain did not differ significantly from the marketed recombinant full-length FVIII product (Advate®). The overall hemodynamic capacity of rVIII-SingleChain appears to be comparable to Advate® when dosed according to

chromogenic FVIII activity. IV administration of rVIII-SingleChain with single doses from 1-150 IU/kg resulted in a dose-dependent correction of hemostasis (total blood loss, time to hemostasis and occurrence of hemostasis). Effects were not worse than those of ReFacto® AF, Helixate® and Advate® when dosed according to chromogenic activity.

4.1.2 Secondary pharmacodynamic studies

No secondary pharmacodynamic studies have been performed

4.1.3 Safety pharmacology programme

There were no treatment related changes to the clinical signs. Furthermore, there were no macroscopic or histopathological changes observed which were considered to be indicative of an effect on the central nervous system.

The electrophysiology of the heart was considered unaffected by rVIII-Single Chain treatment. There were no obvious dose-related effects seen from the observations or the numerical data derived from the electrocardiograms recorded during the course of the study.

4.2 Pharmacokinetic

4.2.1 Single dose PK in FVIII ko mice using the chromogenic assay

Variable	Unit	rVIII-SingleChain	Comparator dose by labeled potency		
		dose by ChS*	Helixate®*	ReFacto AF®*	Advate®*
$C_{max,obs}$	IU/mL	2.31	3.12	2.22	2.21
$AUC_{0.08-72h}$	IU•h/mL	35	31	34	18
AUC	IU•h/mL	37	32	34	18
CL	mL/h/kg	2.74	3.11	2.91	5.53
MRT	h	18	17	14	10
$t_{1/2}$	h	15	15	12	8
Time until 0.05 IU/mL	h	73	68	61	39

- The overall PK properties of rVIII-SingleChain in FVIII ko mice were superior, but did not differ largely from the marketed rFVIII products

4.2.2 Single dose PK in Cynomolgus monkeys after administration of 250 IU/kg using the chromogenic assay

Variable	Unit	rVIII-SingleChain	Comparator dose by labeled potency		
		dose by ChS* APQ0015 / APQ0020	Helixate®* APQ0015	ReFacto AF®* APQ0015	Advate® APQ0020
$C_{max,obs}$	IU/mL	10.74 / 7.49-7.88	11.19	9.92	9.45-7.989
AUC_{24h}	IU•h/mL	101.7 / 77.7-97.2	67.2	78.6	57.50-44.10
AUC	IU•h/mL	125 / 94.7-143.0**	74	93	58.90-45.50
CL	mL/h/kg	2.00	3.39	2.86	4.25-5.49
MRT	h	13.3	8.4	12.2	n.d.
$t_{1/2\beta}$	h	9.7	6.8	9.6	4.6-4.7

- The overall PK properties of rVIII-SingleChain in Cynomolgus monkeys were at least comparable to the marketed rFVIII products Helixate® and ReFacto AF®, and favorable as compared to Advate®.

4.3 Toxicology

4.3.1 Single-dose toxicity studies

rVIII-SingleChain at doses up to 1500 IU/kg was well tolerated in rats and Cynomolgus monkeys. No toxicologically significant changes. NOAEL is 1500 IU/kg for both species.

4.3.2 Repeat-dose toxicity study

Daily intravenous rVIII-SingleChain administration at doses up to 1250 IU/kg/day (rat) or 500 IU/kg/day (monkey) for up to 28 days was well tolerated in both species. No toxicologically significant changes. NOAEL is 1250 IU/kg in the rat and 500 IU/kg in the monkey.

4.3.3 Local tolerance

Intravenous, intra-arterial and perivenous injection of rVIII-SingleChain was well tolerated in the rabbit. No local or systemic (in-life, macropathological and histological) signs of reaction to treatment as compared to isotonic saline treatment used as negative control.

4.3.4 Thrombogenicity

No thrombogenic activity of rVIII-SingleChain at doses up to 500 IU/kg; minimal prothrombotic potential at 1000 IU/kg.

Assessor's conclusions on Non-clinical

Non-clinical data could summarize that study design, number of laboratory animals were suitable and the results were reliable. Toxicity study followed by good laboratory practice. The expert committee meeting on 31st July 2019 summarized in the similarly results as un-redacted assessment report from EMA that overall in non-clinical data was suitable and acceptable.

Part 5: Clinical Study Reports

The Proposed indication of Lonoctocog alfa is indicated for treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). The clinical data can be summarized as below table

Table : Summary of efficacy results from the main studies supporting the present application

No.	Study	Subjective/ Primary Objective	Study design	Intervention	Result
1.	Study 1001: A Phase I/III Open-label, Multicenter, Crossover Safety, Efficacy and Pharmacokinetic Study of Recombinant Coagulation Factor VIII (rFVIII) Compared to Recombinant human antihaemophilic factor VIII (rFVIII; INN: Octocog alfa) in Subjects with Hemophilia A, and a Repeat PK, Safety and Efficacy Study	Characterize the PK profile of rVIII-SingleChain Demonstrate efficacy in prevention and treatment of bleeding episodes Demonstrate efficacy of a routine prophylaxis regimen over on demand regimen Demonstrate efficacy of rVIII-SingleChain in surgical prophylaxis Characterize rate of inhibitor formation	- Phase I / III, prospective multicenter, open label with surgery sub-study (subject 12-65 years) - Duration : 2 years 9 months	**Prophylaxis treatment regimen** - 20 to 50 IU/kg rVIII-SingleChain 2 to 3 times per week. **On-demand treatment of bleeding episodes** - Subjects were treated at a dose pre-determined by the investigator based on the type and severity of the bleeding episode	1. Annualized spontaneous bleeding Rate (AsBR) On-demand : 19.5 Prophylaxis : 1.6 *p-value : <0.0001* 2. Hemostatic efficacy : Treatment success rate from the CSR using primary analysis method. The result has 93.8% for overall treatment success 3. Inhibitor formation to FVIII : 0
2.	Study 3002 : A Phase III Open-	Evaluate efficacy of rVIII-	- Multi-center,	**Prophylaxis treatment**	1. 3002 has an on-demand

	label Pharmacokinetic, Efficacy and Safety Study of rVIII-SingleChain in a Pediatric Population with Severe Hemophilia A	SingleChain in treatment of major and minor bleeding episodes based on investigator 's 4-point assessment scale	open-label, phase III study to assess the efficacy, safety, and PK of Afstyla in subjects 0 to < 12 years of age with severe heamophilia A. - Duration : 1 year, 5 months	**regimen** - 15-50 IU/kg every second day 2 to 3 times per week. **On-demand treatment of bleeding episodes** - Subjects were treated at a dose pre-determined by the investigator based on the type and severity of the bleeding episode	homeostatic efficacy treatment success of 100% in the CSR 2. ABR On-demand : 78.56 Prophylaxis : 3.69 3. Inhibitor formation to FVIII On-demand : 0 Prophylaxis : 0

Clinical studies are divided in 3 parts

1. Clinical Pharmacokinetic

1.1 Compare PK parameter after single injections of rVIII-singleChain or Afstyla and Advate

Parameter, unit	Advate 50 IU/kg (n=26)	rVIII-SingleChain 50 IU/kg (n=26)
C_{max} (IU/dL)	118 (14.8)	114 (16.8)
IR (IU/dL)/(IU/kg)	2.35 (15.0)	1.06 (16.9)
$AUC_{(0\text{-last})}$ (IU*h/dL)	1510 (32.9)	2030 (27.8)
$AUC_{(0\text{-INF})}$ (IU*h/dL)	1580 (34.6)	2130 (29.8)
$T_{1/2}$ (h)	13.4 (33.0)	14.7 (25.4)
CL (mL/h/kg)	3.58 (37.1)	2.64 (32.1)
Vss (mL/kg)	56.2 (18.8)	51.0 (15.9)

Abbreviations: AUC, area under the concentration-time curve; CL, clearance; Cmax, maximum concentration; %CV, percent coefficient of variation; IR, incremental recovery; MRT, mean residence time, PK, pharmacokinetic; t1/2, half-life; Vss, volume of distribution at steady state.
Note: All values are predose-uncorrected, with the exception of IR and Cmax which are presented as predose-corrected.

Result : rVIII-singleChain or Afstyla revealed slightly higher t½ and AUC values whereas the clearance was somewhat reduced in comparison to Advate. These differences are not considered clinically relevant, PK of Afstyla and Advate are comparable.

1.2 Compare PK parameter initial and repeat injection of rVIII-singleChain (Afstyla)

Parameter, unit	Initial (n=64)	Repeat (n=30)
C_{max} (IU/dL)	99.9 (19.9)	108 (17.2)
IR (IU/dL)/(IU/kg)	1.85 (21.8)	1.99 (17.7)
$AUC_{(0\text{-last})}$ (IU*h/dL)	1780 (34.5)	1850 (33.0)
$AUC_{(0\text{-INF})}$ (IU*h/dL)	1830 (34.9)	1880 (34.5)
$T_{1/2}$ (h)	14.1 (27.1)	12.9 (29.4)
CL (mL/h/kg)	3.15 (38.2)	3.05 (36.0)
Vss (mL/kg)	59.5 (23.9)	53.1 (16.4)
MRT (h)	20.3 (26.4)	18.9 (28.5)

Abbreviations: AUC, area under the concentration-time curve; CL, clearance; Cmax, maximum concentration; %CV, percent coefficient of variation; IR, incremental recovery; MRT, mean residence time, PK, pharmacokinetic; t1/2, half-life; Vss, volume of distribution at steady state.
Note: All values are predose-uncorrected, with the exception of IR and Cmax which are presented as predose-corrected.

Result : Single PK initial and repeat of Afstyla are comparable

1.3 PK Parameters comparing subjects by age group after initial injection of Afstyla for subjects (50 IU/kg)

Parameter (units)	Adults [12, 13] 18 to ≤65 years ($n = 81$)	Adolescents [12, 13] 12 to <18 years ($n = 10$)	Children [8]	
			6 to <12 years ($n = 19$)	0 to <6 years ($n = 20$)
AUC_{∞} (IU·h/dL)	1960	1540	1170	1080
CL (mL/h/kg)	2.90	3.80	4.63	5.07
C_{max} (IU/dL)	106.0	89.70	83.50	80.20
IR (IU/dL per IU/kg)	2.00	1.69	1.66	1.60
MRT (h)	20.40	20.00	12.30	12.40
$t_{1/2}$ (h)	14.20	14.30	10.20	10.40
V_{ss} (mL/kg)	55.2	68.50	67.10	71.00

FVIII activity assessed using a chromogenic substrate assay; all values are means

AUC_{∞} area under the FVIII activity-time curve extrapolated to infinity, *CL* clearance, *C_{max}* maximum concentration, *FVIII* factor VIII, *IR* incremental recovery, *MRT* mean residence time, *$t_{1/2}$* elimination half-life, *Vss* volume of distribution at steady state

Result : PK parameters of subjects 12-18 years and subjects 18-65 years were similar. Mean CL was higher in subjects 0-12 years than in subjects 12 – 65 years, with consequently lower mean AUC and half-life values.

2. Clinical efficacy

There are 2 pivotal studies to support proposed indication, Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). The outcome in each studies are annualised spontaneous bleeding rate and treatment success rate.

2.1 ***Study in adult patient (12-65 years old)***

2.1.1 Study 1001 : A Phase I/III open-label, multicenter, crossover safety, efficacy and pharmacokinetic study of recombinant coagulation factor VIII (rFVIII) compared to recombinant human antihaemophilic factor VIII (Octocog alfa) in subjects with hemophilia A, and a repeat PK, safety and efficacy study

Objectives : The objective of this study was to evaluate the efficacy, safety, and pharmacokinetic of rFVIII single-chain relative to Octocog alfa in patients with heamophillia A.

Outcomes/endpoints : The primary efficacy was annualized spontaneous bleeding rate (AsBR) and hemostatic efficacy in the control to bleeding episodes and during surgery. Secondary efficacy endpoints were annualized bleeding rate (ABR) and number of injections required to achieve hemostasis.

The results :

1. Annualized spontaneous bleeding rate between on-demand and prophylaxis group

	On-demand (N=27)	**Prophylaxis** (N= 146)
Spontaneous bleeding episode		
No. of bleeding episode per year (95% CI)	11.73 (**28**, 36.5)	1.14 (**0,4.2**)
Total bleeding episode		
No. of bleeding episode per year (95% CI)	24.9 (23.0, 27.0)	2.6 (2.3, 2.9)

Summary : AsBR, ABR in subject on prophylaxis regimen was significant lower

(p<0.0001) than in subject on demand group

2. Overall Investigator's Assessment of Hemostatic Efficacy

Bleeding type assessment	On-demand (N=27)	Prophylaxis (N=146)	Overall (N=173)
Number of bleeding episodes	594	278	872
Number of treated bleeding episodes	590	258	848
Excellent (n [%])	421 (71.4)	182 (70.5)	603 (71.1)
Good	124 (21.0)	56 (21.7)	180 (21.2)
Moderate	32 (5.4)	20 (7.8)	52 (6.1)
Poor/ no response	0	0	0
Missing	13 (2.2)	0	13 (1.5)
Rate of treatment success	92.4	92.2	92.3

Summary : Most patients response in good or excellent scale. The rate of treatment success was similar between treatment regimens on-demand and prophylaxis. Overall treatment success is around 92.3-93.9%.

2.2 Study in pediatrics (< 12 years old)

2.2.1 Study 3002 : A Phase III open-label pharmacokinetic, efficacy and safety study of rVIII-SingleChain in a pediatric population with severe hemophilia A.

Objectives : The objective of this study was to evaluate the efficacy, safety, and pharmacokinetic of rFVIII single-chain relative to Octocog alfa in pediatric with heamophillia A.

Outcomes/endpoints : The primary efficacy was annualized bleeding rate and treatment success rate.

The results :

1. Annualized bleeding rate between on-demand and prophylaxis group

	On-demand	Prophylaxis
ABR for total bleeds median (Inter-Quartile Range)	**78.56 (35.12 to 86.62)**	**3.69 (0.00 to 7.20)**

Summary : ABR in subject on prophylaxis regimen was lower than in subject on demand group

2. Overall Investigator's Assessment of Hemostatic Efficacy

Bleeding type assessment	On-demand (N=27)	Prophylaxis (N=146)	Overall (N=173)
Number of bleeding episodes	133	256	389
Number of treated bleeding episodes	132	215	347
Excellent (n [%])	132 (100.0)	164 (76.3)	296 (85.3)

Good	0	38 (17.7)	38 (11.0)
Moderate	0	12 (5.6)	12 (3.5)
Poor/ no response	0	1 (0.5)	1 (0.3)
Rate of treatment success	100	94.0	96.3

Summary : Most patients response in good or excellent scale. The rate of treatment success was similar between treatment regimens on-demand and prophylaxis. Overall treatment success is around 96.3%.

3. Clinical safety

3.1 The most common adverse event of each studies can summarize as :

Study	Most common TEAEs
Study 1001	nasopharyngitis, arthralgia and headache
Study 3002	nasopharyngitis, arthralgia, cough, and headache

3.2 No subject developed an inhibitor under exposure to rVIII-SingleChain in any of the studies.

3.3 In study 1001, 2 subjects (1.1%) experienced hypersensitivity reactions.
In study 3002, the related event of hypersensitivity was mild in intensity and the dose of rVIII-SingleChain was not changed as a result of this event.

3.4 In PSUR ; no case report in PTPs occur developed inhibitor.

Assessor's conclusions on clinical

Clinical pharmacokinetic, efficacy and safety studies have appropriate study design, population and duration for proposed indication "Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency)". The most common adverse events are nasopharyngitis, arthralgia and headache. The clinical data is acceptable which is consistency with unredacted assessment report from EMA. There is enough evidence to support efficacy and safety of Afstyla for treatment and prophylaxis bleeding in haemophilia A patient. The risk to develop an inhibitor event that occurs under exposure to rVIII-SingleChain need to be closely monitored in extension study and post-marketing study.

Part 6: Risk Management Plan

The information of RMP is valid and suitable due to the risk management had been conducted in summary of product characteristic and patient leaflet already.

Label evaluation

Registered label from Zuellig pharma Ltd, is Unit carton label and inner label following Thai FDA 2009 ANNEX 3 Package insert and labeling rule.

UNIT CARTON

No.	Topic	Available	Appropriate
1	Product name	✓	✓
2	Dosage form	✓	✓
3	Name of Active Ingredients	✓	✓
4	Strength of Active Ingredients	✓	✓
5	Batch Number	✓	✓
6	Manufacturing date	✓	✓
7	Expiration date	✓	✓
8	Route of Administration	✓	✓
9	Storage condition	✓	✓
10	Country's Registration Number	✓	✓
11	Name and address of Marketing Authorization Holder	✓	✓
12	Name and address of manufacturer	✓	✓
13	Special labeling	✓	✓
14	Recommended Daily Allowance (Vitamins and minerals)	n/a	n/a
15	Warning	✓	✓
16	Pack sizes	✓	✓

✓ Available or appropiate

n/a not available

Inner label

No	Topic	Available	Appropiate
1	Product name	✓	✓
2	Name of Active Ingredients	✓	✓
3	Strength of Active Ingredients	✓	✓
4	Batch Number	✓	✓
5	Expiration date	✓	✓
6	Route of administration	✓	✓

✓ Available or appropriate

n/a not available

Inner label (Sterile water for injection 2.5 ml and 5 ml)

No	Topic	Available	Appropiate
1	Product name	✓	✓
2	Name of Active Ingredients	✓	✓
3	Strength of Active Ingredients	✓	✓
4	Batch Number	✓	✓
5	Expiration date	✓	✓
6	Route of administration	✓	✓

✓ Available or appropriate

n/a not available

Patient information leaflet (PIL) evaluation

Patient information leaflet of Lonoctocog alfa is adapted from SmPC and the originator SmPC. The information in Patient information leaflet is accurate, complete, and consistency with SmPC, quality data, non-clinical data and clinical data. The important information for patient is summarized in this PIL, however, user testing in Thais is required 12 months after receiving registered paper.

Summary of product characteristics (SmPC) evaluation

Summary of product characteristics conform to quality, non-clinical and clinical supporting data. The important information for healthcare professional is summarized in this SmPC, promotes rational drug use.

Overall Benefit/risk assessment

The documents submitted to support the quality, efficacy and safety of Lonoctocog alfa are appropriate and acceptable. The quality of Lonoctocog alfa is acceptable and pass the standard criteria, non-clinical and clinical data supported proposed indication and no serious adverse event especially developed inhibitor or immunogenicity events reported during study through post-marketing. However, the risk to develop an inhibitor event that occurs under exposure to rVIII-SingleChain need to be closely monitored in extension study and post-marketing study.

The evaluation results of un-redacted assessment report from EMA and Thai advisory expert committee on 31st July 2019 are consistency, overall benefit/risk assessment is positive, so all can summarized Afstyla powder and solvent for solution for injection registered indication below is acceptable for treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency) with conditions as follows

1) This medicine will only be prescribed in hospitals and clinics.

2) Follow the adverse event in post-marketing conducted by SMP protocol submitted in eCTD.

3) Submit the complete version of PIL after the user testing passes the criteria (user testing result should be submitted to Thai FDA within 12 months after the marketing authorization approval).

4. Submit data and follow by proposed risk management plan in 1.8.2 Risk management system on eCTD, as shown in appendix 1.

Reference

1. Bowen DJ. Haemophilia A and haemophilia B: molecular insights. Mol Pathol. 2002;55(1):1–18. doi:10.1136/mp.55.1.1

2. Hemophilia WFo. Guidelines for the management of hemophilia. 2012 (Prophylactic factor replacement therapy):12.

3. นพ. นัทธี นาคบุญนำ. แนวทางการรักษาผู้ป่วยฮีโมฟีเลียในประเทศไทย. (Hematology and oncology guideline).

Appendix 1

(Risk management plan)

Appendix 1

Risk Management Plan (RMP)) for Afstyla, can conclude as;

Areas requiring confirmation or further investigation	Proposed routine and additional PV activities	Objectives
Safety concern: Important Identified Risk – Hypersensitivity and anaphylactic reactions		
Nature, severity, latency from first use of rVIII-SingleChain, risk factors and outcome of hypersensitivity/anaphylactic reactions.	Routine PV including additional follow-up and specific follow-up questionnaire.	Further characterize incidence, nature, severity and outcome.
	Study 3001 (including enrolment of PUPs).	To provide further safety and efficacy data in patients.
Safety concern: Important Identified Risk – Development of inhibitors		
Latency from first use of rVIII-SingleChain, risk factors and outcome of FVIII inhibitor development	Routine PV including additional follow-up and specific follow-up questionnaire.	Further characterize incidence, nature, severity and outcome.
	Study 3001 (including enrolment of PUPs).	To provide further safety and efficacy data in patients.
Safety concern: Important Potential Risk – Dosing errors based on assay type (Chs vs OS) used for monitoring of FVIII levels		
Prompt identification of dosing error in patients	Routine PV	Further characterize incidence, nature, severity and outcome.
Safety concern: Important Potential Risk – Development of antibodies against CHO host cell proteins		
Latency from first use of rVIII- SingleChain, risk factors and outcome of antibodies against CHO host cell proteins	Routine PV	Further characterize incidence, nature, severity and outcome.
	Study 3001(including enrolment of PUPs).	To provide further safety and efficacy data in patients.
Safety concern: Missing Information – Experience of inhibitor formation in PUPs		
Latency from first use of rVIII SingleChain, risk factors and outcome of inhibitor development in PUPs	Routine PV including additional follow-up and specific follow-up questionnaire.	Further characterize incidence, nature, severity and outcome.
	Study 3001 (including enrolment of PUPs).	To provide further safety and efficacy data in patients.
Safety concern: Missing Information – Experience in pregnancy and lactation, including labor and delivery		
Usage and safety in pregnancy/labor/lactation	Routine PV including pregnancy follow-up questionnaire.	Further characterize incidence, nature, severity and outcome.
Safety concern: Missing Information – Experience in geriatric patients (65 years and above)		
Usage and safety in geriatric patients	Routine PV	Further characterize incidence, nature, severity and outcome.

AE: adverse events; CHO: Chinese hamster ovary; ChS: chromogenic substrate; OS: one-stage; rVIII-SingleChain; PUP: previously untreated patients; PV: pharmacovigilance.

* Study 3001 : A Phase III Open Label, Multicenter, Extension Study to Assess the Safety and Efficacy of Recombinant Coagulation Factor VIII (rVIII-SingleChain,CSL627) in Subjects with Severe Hemophilia A

Table 21: Required Additional Pharmacovigilance Activities

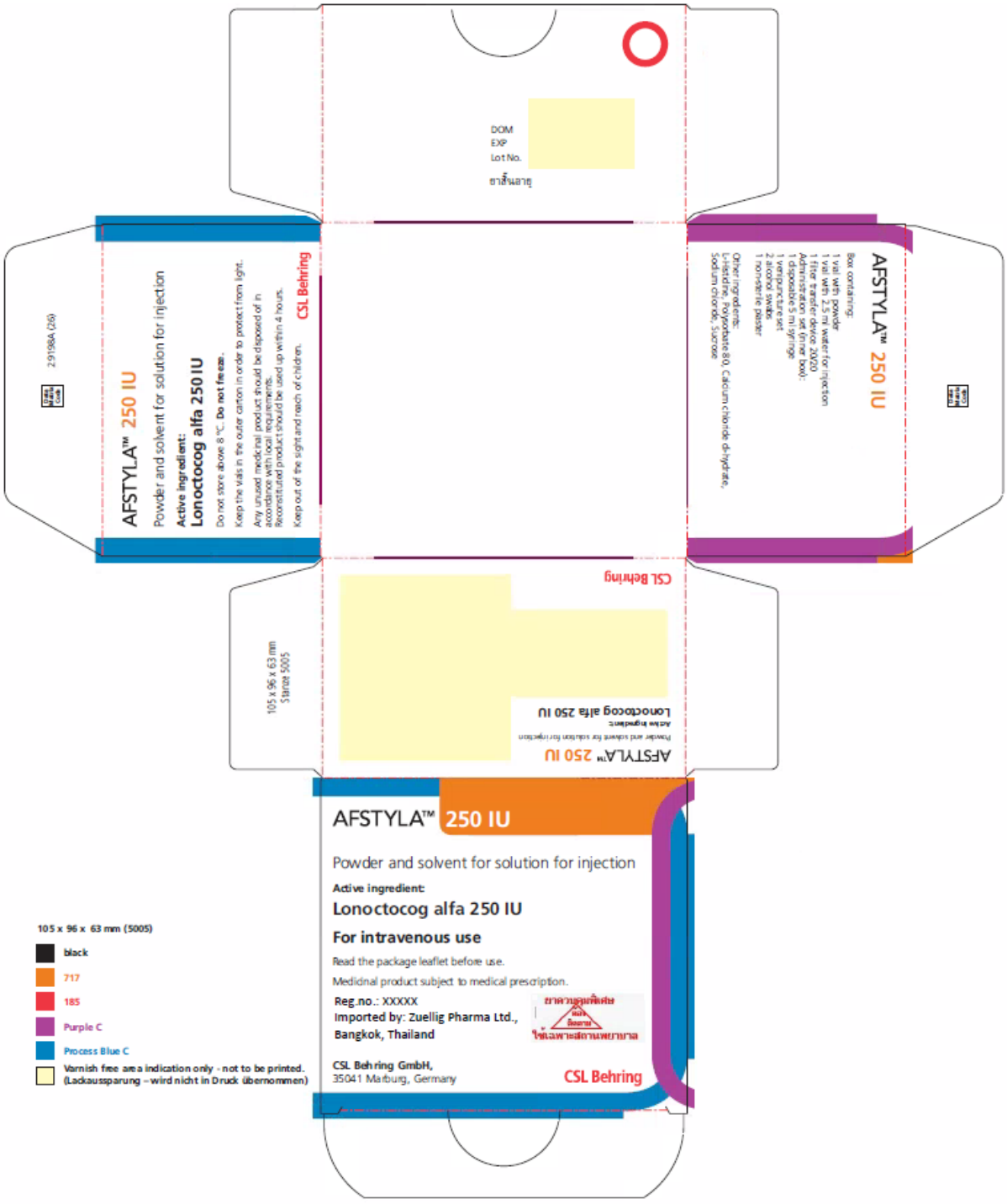
Description of study (including objectives and study number)	Milestones	Due dates
Study 3001 A phase III open label, multicenter, extension study to assess the safety and efficacy recombinant coagulation Factor VIII (rVIII-SingleChain, CSL627) in subjects with severe hemophilia A, including PUPs.	Final protocol	19 September 2013
	Protocol amendment #1	28 March 2014
	Protocol amendment #2 (ie, to include a separate study arm for PUPs)	05 June 2015
	Study start	13 October 2014 (first subject in).
	Interim report	Interim "snapshot" for 200 PTPs with 100 ED: Q2 2017
	Study finish	Q3 2021
	Final report	Anticipated Q4 2021.

ED: exposure days; FVIII: coagulation factor VIII; MAA: marketing authorization application; PUPs: previously untreated patients; rVIII-SingleChain: Recombinant Single-Chain Factor VIII.

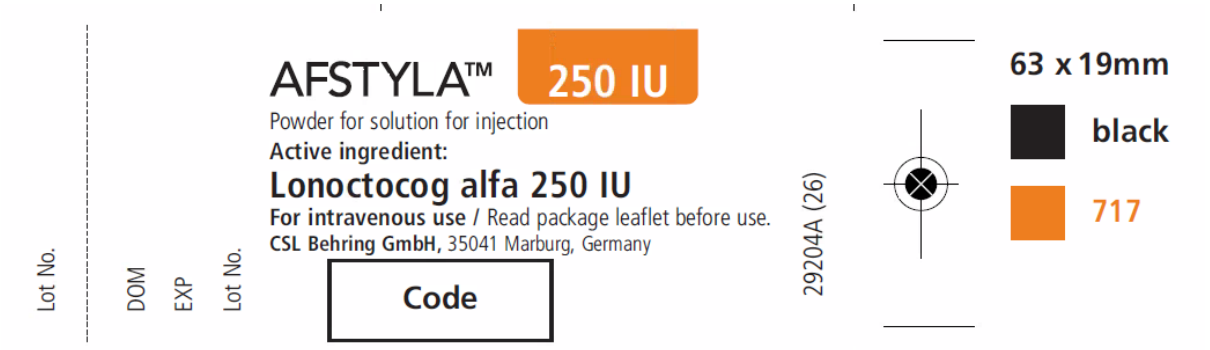
Appendix 2

(Labeling)

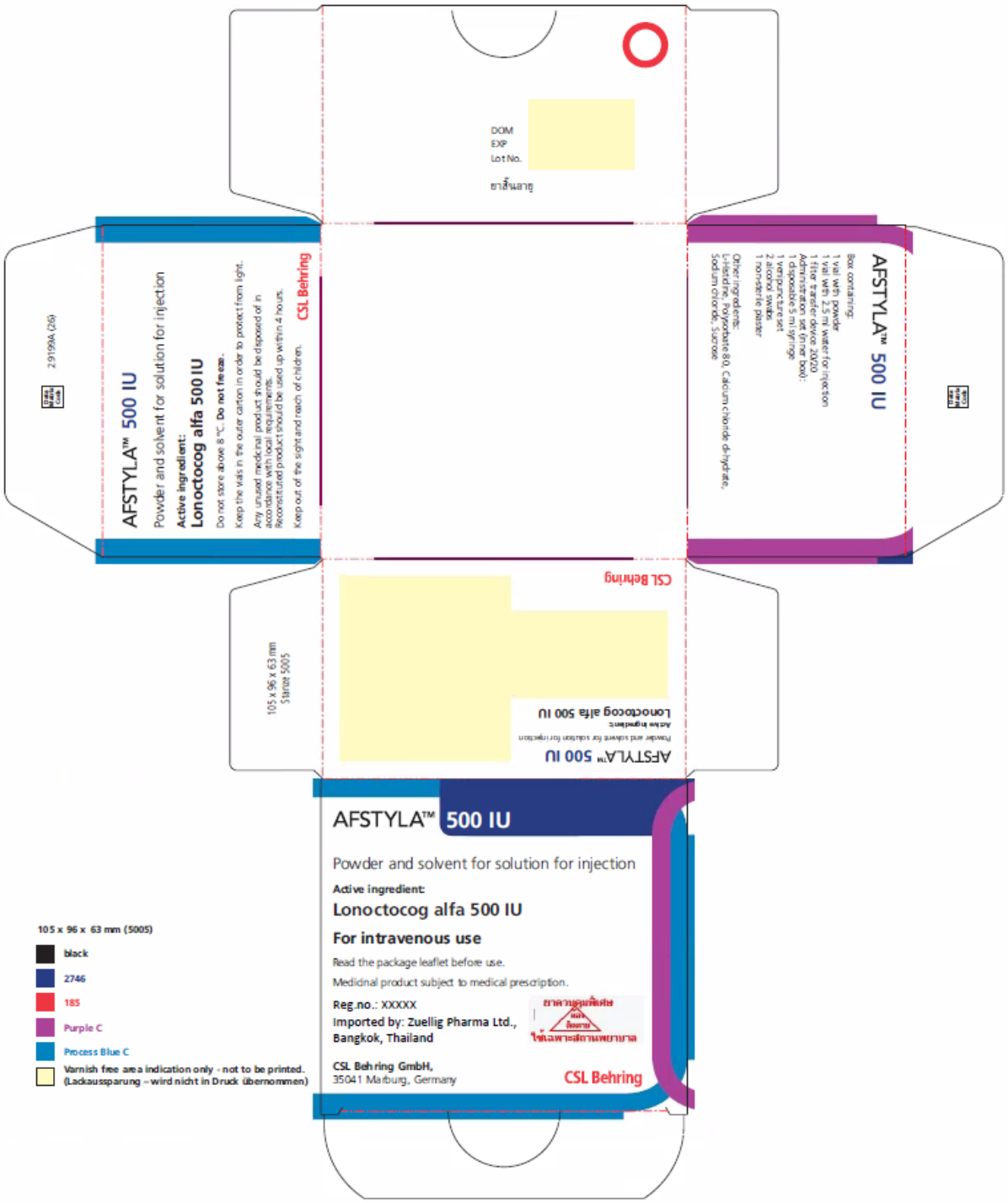
Unit carton : Afstyla 250 IU



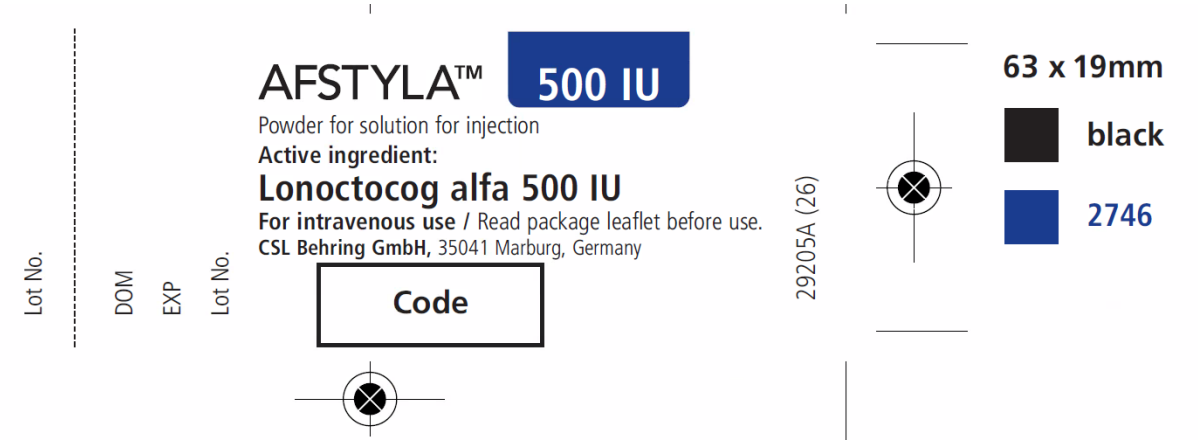
Inner label : Afstyla 250 IU



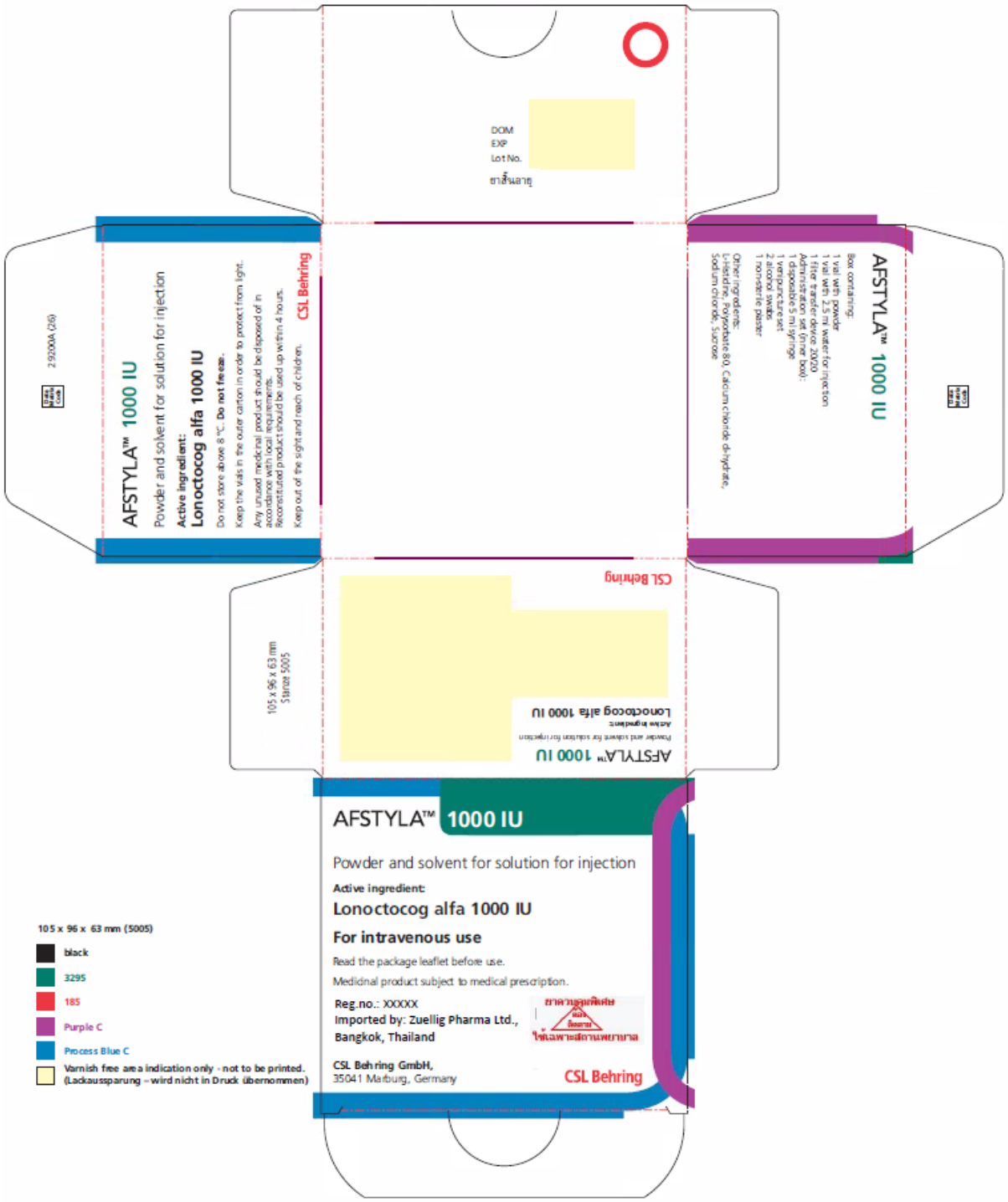
Unit carton : Afstyla 500 IU



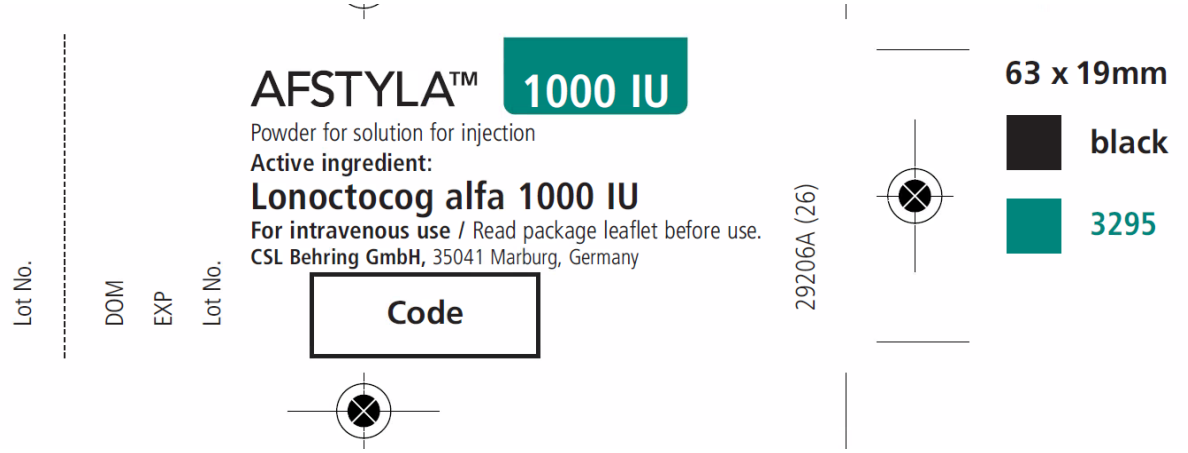
Inner label : Afstyla 500 IU



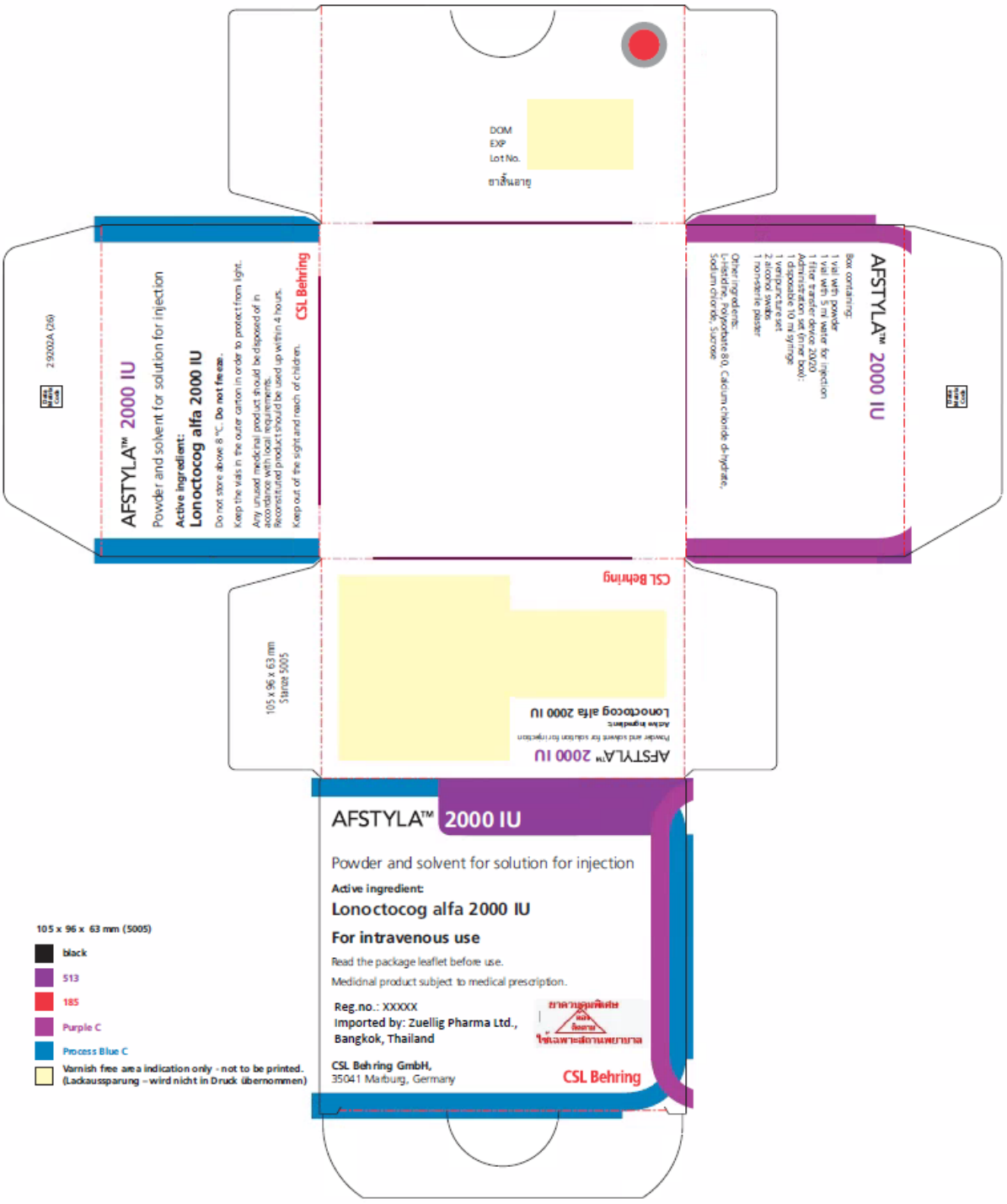
Unit carton : Afstyla 1000 IU



Inner label : Afstyla 1000 IU



Unit carton : Afstyla 2000 IU



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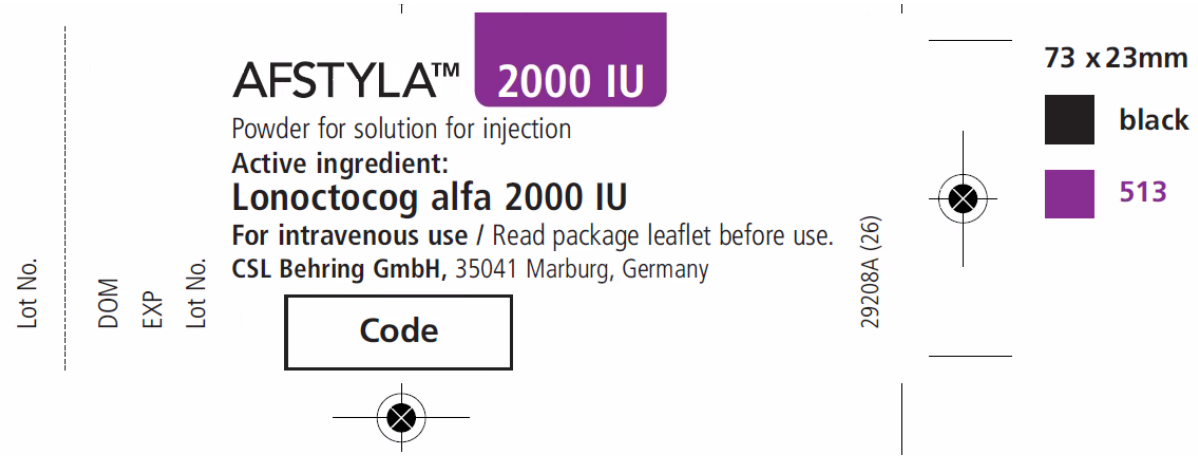
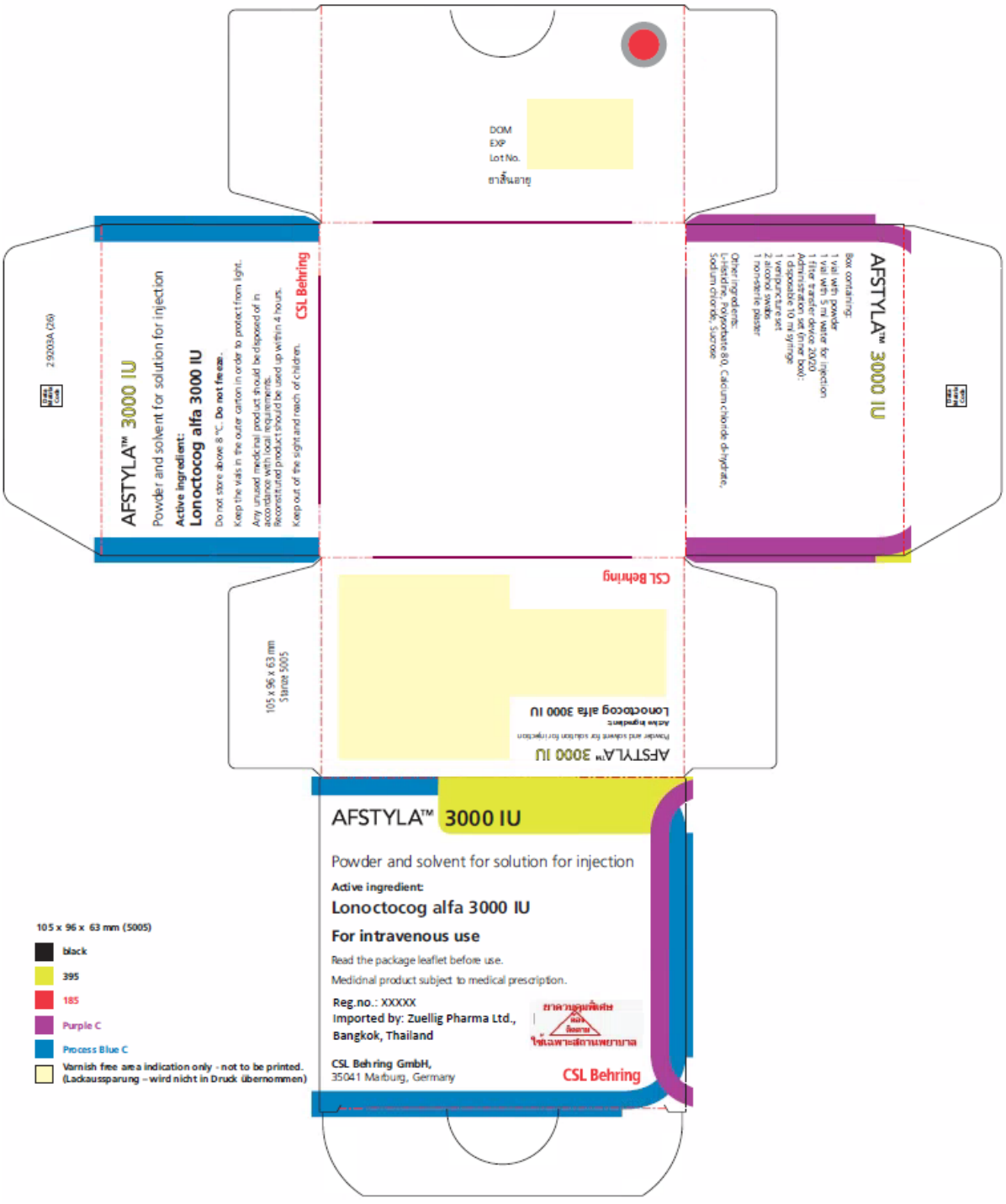
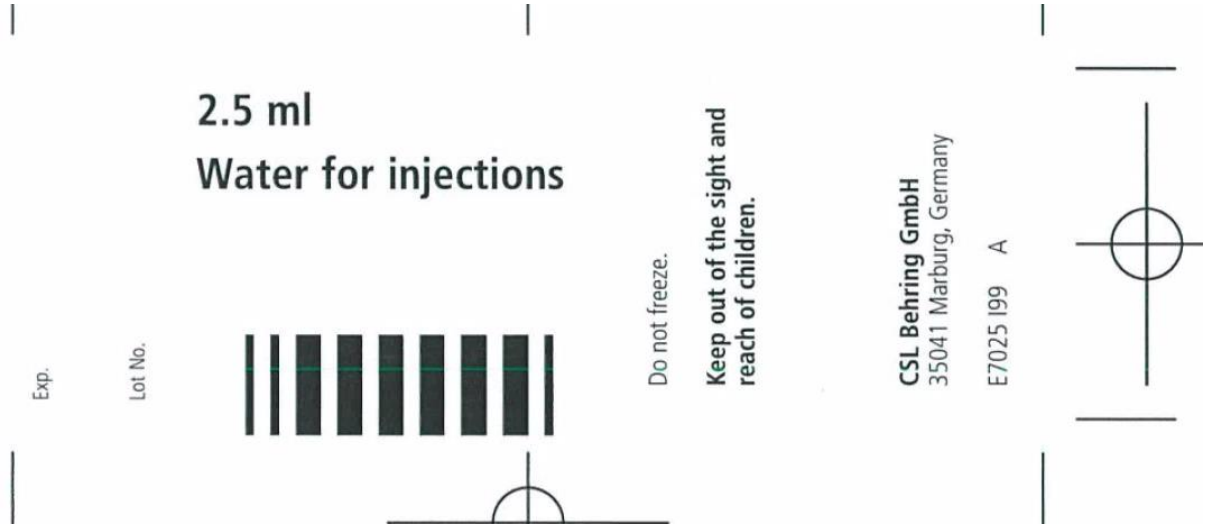


Unit carton : Afstyla 3000 IU



Inner label : Afstyla 3000 IU

Inner label : Sterile water for injection 2.5 ml



Inner label : Sterile water for injection 5 ml