To:

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Notification of discontinuation of a paediatric development which is covered by an agreed PIP Decision

Actives substances(s): N-Acetyl-L-Cysteine (corresponds to L-Cysteine), I,-Alanine, L-Alanyl-L-Glutamine (corresponds to L-Alanine and L-Glutamine), L-Arginine hydrochloride (corresponds to L-Arginine), Glycine, Glycyl-L-Tyrosine (corresponds to Glycine and L-Tyrosine), L-Histidine, L-Isoleucine, L-Leucine, I,-Lysine acetate (corresponds to L-Lysine), L-Methionine, L-Phenylalanine, L-Proline, L-Serine, Taurine, L-Threonine, L-Tryptophan, L-Valine

Invented name: Neoven

Latest Decision number(s): 1) P/175/2009/ 2) P/ 3) P/ 4) P/

Corresponding PIP number(s): 1) EMEA-000042-PIP01-07-M01 2) EMEA- 3) EMEA- 4) EMEA-

Please note that development of the medicinal product above in the [condition(s)/indication(s)]:

Supply of essential and non-essential amino acids as part of parenteral nutrition for pre-term and full-term neonates, infants and children, when oral or enteral nutrition is impossible, insufficient or contraindicated.

☒ has been discontinued

☐ has been suspended/put on long-term hold (with possible re-start at a later time)

for the following reason(s): (tick all that apply)

☐ (possible) lack of efficacy in adults

☐ (possible) lack of efficacy in children

☐ (possible) unsatisfactory safety profile in adults

☐ (possible) unsatisfactory safety profile in children

☐ commercial reasons (please specify:)

☐ manufacturing / quality problems

☐ other regulatory action (please specify:) (e.g. suspension, revocation of M.A.)

☒ other reason (please specify:)

Please add a brief description (max 2000 characters) of the reason(s) for the discontinuation / suspension:

Unfortunately, we had to realise that the provided study protocols do not sufficiently reflect the clinical routine for the NEOVEN 002 and 003 studies and even though enormous efforts were undertaken to ensure appropriate recruitment rates, our expectations could not be met. Further adjustment in order to achieve the originally intended goal would lead to the necessity of a significant protocol amendment, which would be considered from an authority point of view as a new clinical trial.

The clinical trials are based upon several binding regulatory documents, where the Paediatric Investigational Plan is one part. With a current recruitment rate of 1,3 patients/month and a target number of 100 patients in NEOVEN 002 and a recruitment rate of 0,5 patients/month and a target number of 80 patients in NEOVEN 003, it will not be possible to complete the trial within the time frame agreed in the PIP. Additionally, as the achievement of the requested patient number is jeopardized, this might impact on the outcome of the whole clinical study program.

For the NEOVEN study 004, corresponding resources were allocated for a time frame that was communicated towards authorities, trial sites and Key Opinion Leaders became part of the corresponding regulatory binding document like the Paediatric Investigational Plan (PIP).

NEOVEN 004 is a clinical trial exclusively conducted in France. Due to the special situation in France, we were obliged to use the French non-investigational medicinal products (NIMPS), i.e. trace elements from Aguettant. Shortly after the study commenced, quality problems with these trace elements had been reported by the supplier. Replacement medication (DECAN) from the same supplier had to be authorized and the study was set on hold by AFSSAPS. The clarification of the before mentioned issue has caused a delay of 4 month.

As agreed earlier, Fresenius Kabi would have to apply for a regulatory permission to use PEDITRACE, since the use of DECAN would possibly lead to the risk of similar availability problems as we had before with “Oligo Elements des Enfants” (both from Aguettant). The PEDITRACE submission would have lead to a further delay.

Against the background of the significant unforeseeable delay and the uncertainty of NIMPs availability, it is not possible to complete the trial within the time frame agreed with the authorities in the PIP. The mandatory logistical adaptations influencing the study set-up and leading to the necessity of significant protocol changes will probably be considered from authorities as set up of a new clinical study.

For study 002 and 004 an evaluation of DSMB was performed and based on the patient data being available and reviewed by the Data Safety Monitoring Board (DSMB) on the 15 February 2011, the DSMB members came to the conclusion that there is no important risk for the patients participating in the clinical trial and that the clinical trial could continue without amending the protocol or the parent information and informed consent form under safety considerations.

The early termination of the clinical trial was not due to reasons of safety.

We want to confirm that data of all patients being enrolled so far will be evaluated and reported according to ICH-GCP Guidelines, national/international standards, and ethical principles of medical research involving human subjects. All the information (data) collected from the patients during the course of this study will be kept strictly confidential and will only be used as part of the clinical study in accordance with applicable data protection rules.

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