Sundhedsstyrelsen
Danish Health and Medicines Authority

Att.: Morten Hylander Møller
Rigshospitalet
Blegdamsvej 9
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"Stress ulcer prophylaxis with proton pump inhibitor (pantoprazole) in adult critically ill patients in the intensive care unit", protocol no. RH-ITA-006, EudraCT-no. 2015-000318-24.

June 8, 2015

Case no: 2015030166

Reference: Katja Magnussen

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Decision:

The Danish Health and Medicines Authority hereby authorises the conduct of the above-mentioned clinical trial on medicinal products, cf. section 88(1) of the Danish Medicines Act.[1]

The authorisation is valid up to and including **November 1, 2017.**

The trial covers the following investigational medicinal products:

- Pantoprazol
- Placebo

It is a condition for the authorisation that we are **notified** of any of the following events:

- Trial duration is extended beyond the date in authorisation letter
- Addition of new investigator sites (incl. an updated xml-file)
- Changes of principal/coordinating investigator (incl. an updated xml-file)
- Changes of CRO/applicant
- National end of trial

[1] Danish act no. 1180 of 12 December 2005 on medicinal products as amended by act no. 538 of 8 June 2006 and act no. 1557 of 20 December 2006

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On the webpage http://laegemiddelstyrelsen.dk/en/topics/side-effects-and-trials/clinical-trials/trials-in-humans/guideline-for-applications-for-authorisa---in-humans/amendments-to-clinical-trials-.aspx you will find a summary of the changes that we consider substantial and therefore must be approved by us.

The Danish Health and Medicines Authority has based its assessment on the following:

Documents:

- Cover letter, dated 01.03.2015
- EudraCT application form, signed 27.04.2015, PDF and XML-file
- SUP protocol, version 2.0, dated 22.04.2015
- Danish protocol resume, version 1.2, dated 13.05.2015
- Subject information (patient), version 1.1, dated 17.03.2015
- Informed consent form (patient), version 1.0, dated 25.02.2015
- Subject information (relatives), version 1.1, dated 17.03.2015
- Informed consent form (relatives), version 1.0, dated 25.02.2015
- Subject information (guardian), version 1.1, dated 17.03.2015
- Informed consent (guardian), version 1.0, dated 25.02.2015
- Procedure for giving subject information, version 1.1, dated 17.03.2015
- SmPC for Pantoprazol, Actavis
- Billing information
- Orientation letter to manufacturer, Actavis
- Response letter, dated 23.04.2015

Prior to initiation of the trial it has to be authorised by a research ethics committee.

We kindly refer to the enclosed extract of the Danish legislation.

Kindly address any further questions to M.Sc. Katja Magnussen
T (dir.) +45 44 88 92 43
Email: KMAG@dkma.dk

Best regards,

Katja Magnussen

Copy: The Regional Scientific Ethical Committees for the Capitol Region.

Legal obligations related to the conduct of clinical trials on medicinal products

Good clinical practice (GCP)
Clinical trials on medicinal products must be conducted in accordance with good clinical practice, cf. section 88(2) of the Danish Medicines Act[2], and the Danish executive order on good clinical practice in clinical trials of medicinal products in humans[3].

Good manufacturing practice (GMP)
The medicinal products of clinical trials must comply with the current standards for good manufacturing practice, cf. section 92(1) of the Danish Medicines Act, and the Danish executive order on the manufacturing and import of medicinal products and intermediary products. Investigational medicinal products manufactured in or imported from a third country (a non EU/EEA country) must comply with good manufacturing standards (at least equivalent to EU GMP).
In order to ensure that the investigational products manufactured in a third country comply with EU GMP or similar requirements, it is the practice of the Danish Medicines Agency to require that documents in support thereof be made available on request. This could be in the form of a GMP certificate issued by an EU authority and/or an EU GMP audit report from a Qualified Person and/or other EU GMP report issued by a regulatory body. This also applies to sites that manufacture active biological substances. In the case of countries with mutual recognition agreements (Canada, Switzerland, Australia and new Zealand) the above documents may be replaced by a GMP certificate and/or manufacturing licence issued by a regulatory body in the concerned MRA country.

Good distribution practice (GDP)
Distribution of medicinal products to sites must be in accordance with GDP i.e. the Danish executive order on distribution of medicinal products. The Danish Health and Medicines Authority must authorise wholesale or retail distribution of medicinal products, i.e. distribution of medicinal products, cf. section 39(1) of the Danish Medicines Act.

Free provision of test products
Investigational medicinal products and any devices used to administer investigational medicinal products must be supplied free of charge to trial subjects, cf. section 13 of the Danish executive order on good clinical practice in clinical trials of medicinal products in humans.

Amendments to clinical trials
Section 4 of the Danish executive order on clinical trials of medicinal products in humans establishes when amendments to a clinical trial require authorisation from the Danish Medicines Agency. Please also see 'Amendments to clinical trials' available on our website www.dkma.dk .

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[2] Danish act no. 1180 of 12 December 2005 on medicinal products as amended by act no. 538 of 8 June 2006 and act no. 1557 of 20 December 2006

[3]Danish executive order no. 744 of 29 June 2006 on good clinical practice in clinical trials of medicinal products in humans (Danish title: Bekendtgørelse nr. 744 af 29. juni 2006 om god klinisk praksis i forbindelse med kliniske forsøg med lægemidler på mennesker).

Direct link: http://laegemiddelstyrelsen.dk/en/topics/side-effects-and-trials/clinical-trials/trials-in-humans/guideline-for-applications-for-authorisa---in-humans/amendments-to-clinical-trials-.aspx

Reporting of adverse reactions occurring during the trial period

The sponsor must

- *immediately* inform the Danish Medicines Agency of any suspected unexpected serious adverse reactions that occur during the trial.
- once a year submit a list of all suspected serious adverse reactions that have occurred during the trial period as well as a report on the safety of the trial subjects, cf. section 89 (2) of the Danish Medicines Act.

Termination of a trial

The sponsor must

- notify the Danish Medicines Agency when the trial has been completed (no later than 90 days thereafter),
- inform the Danish Medicines Agency (within 15 days) if a trial is discontinued earlier than planned. The reasons for stopping the trial must be given cf. 89 of the Danish Medicines Act.

Study results

- Results should be reported to the EudraCT database as soon as possible and no later than one year after end of trial according to http://ec.europa.eu/health/files/eudralex/vol-10/2012_302-03/2012_302-03_en.pdf.
- The DHMA do not wish to be informed about this or receive the final study report. The DHMA will review the EudraCT database regarding study results.