PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

DraxImage MDP powder for solution for injection 10 mg
DRAxIMAGE (UK) Limited, United Kingdom

medronic acid (MDP)

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.

It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.

This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB’s knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/962/001/MR
Registration number in the Netherlands: RVG 57717

29 April 2010

Pharmacotherapeutic group: Diagnostic radiopharmaceuticals; skeleton; technetium (99mTc) compounds
ATC code: V09BA02
Route of administration: Parenteral
Therapeutic indication: After reconstitution with sodium pertechnetate (99mTc) solution; bone scintigraphy for the detection of areas of altered osteogenesis associated with neoplasms and non-neoplastic lesions.

Prescription status: prescription only
Date of first authorisation in NL: 29 March 2006
Concerned Member States: Mutual recognition procedure with AT, BE, CZ, DE, DK, ES, FR, IE, IT, PL, PT, and UK.
Application type/legal basis: Directive 2001/83/EC, Article 10(a)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.
I  INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for DraxImage MDP powder for solution for injection 10 mg, from DRAXIMAGE (UK) Limited. The date of authorisation was on 29 March 2006 in the Netherlands. Prior to this registration, the product has been on the Dutch market for more than 10 years. This was allowed on special conditions, under the schedule of “old” established Radiopharmaceuticals.

After reconstitution with sodium pertechnetate ($^{99m}$Tc) solution, the agent is used for bone scintigraphy for the detection of areas of altered osteogenesis associated with:

**Neoplasms:**
- The detection, staging, and evaluation of response to therapy of primary bone tumors (e.g. Ewing’s sarcoma, osteosarcoma)
- The detection and follow-up of bone metastases

**Non-neoplastic lesions:**
- As an aid in the evaluation of:
  - Osteomyelitis
  - Avascular necrosis
  - Paget’s disease
  - Stress fractures, shin splints
  - Loose or infected joint prosthesis
  - Reflex sympathetic syndrome
  - Bone graft viability

Since areas or altered osteogenesis can be detected with high sensitivity but low specificity, additional examinations may be necessary. A comprehensive description of the indications and posology is given in the SPC.

Diphosphonates are analogs of pyrophosphate, a normal constituent of bone. Their distribution in bone mimics that of pyrophosphate, accumulating in actively growing bone in the metaphyses adjacent to the epiphyses along endosteal and periosteal surfaces and trabeculae, rather than in dense, compact bone. $^{99m}$Tc-MDP is thought to separate into its technetium and methylene diphosphonate components in the bone. The technetium is preferentially taken-up by the newly formed osteoid, while the methylene diphosphonate is taken up by the forming mineral.

At the milligram dose of $^{99m}$Tc-medronate administered for diagnostic procedures, $^{99m}$Tc-medronate does not exert any pharmacodynamic effects.

The marketing authorisation is granted based on article 10a of Directive 2001/83/EC, well-established use. This application concerns a bibliographical application based on well-established medicinal use of medronate. This type of application does not require submission of the results of pre-clinical tests or clinical trials if the applicant can demonstrate that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety. “Medicinal use” does not exclusively mean “use as an authorised medicinal product”, so that the proof of medicinal use may be submitted even in the absence of a marketing authorisation. Well-established use refers to the use for a specific therapeutic use. For this kind of application, a detailed description of the strategy used for the search of published literature and the justification for inclusion of the references in the application has to be provided. The documentation submitted by the applicant should cover all aspects of the assessment and must include a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies.

In the early nineties, a coordinated European procedure has taken place to register Radiopharmaceuticals already on the market for years in the European Member States. This procedure was initiated, as it had become mandatory to register this category of medicinal products after a change in the European
legislation. At that time, it was agreed upon by the Member States to accept a “core” clinical expert report per active substance, in which the therapeutic field and safety issues had to be sufficiently discussed. The “core” SPC of the active substance would be based on the approved expert report of this substance. These expert reports were made in cooperation with several manufacturers/applicants of the Radiopharmaceuticals in question, working together in their society “ARPE”. Given the fact that these products had been on the market for years, a preclinical expert report was not deemed necessary. With respect to the chemical pharmaceutical part of the dossiers, assessments for each individual product from a certain manufacturer were of course performed. This procedure would allow marketing authorisation of a particular radiopharmaceutical in all Member States involved.

The product under consideration was withdrawn from the above mentioned combined procedure. Therefore, a marketing authorisation for DraxImage MDP was not applied for in the Member States at that time. The current MAH DRAXIMAGE (UK) Limited does have the wish to market the product also outside the Netherlands. Therefore, the MAH has provided a new and updated Module 2 together with new preclinical and clinical overviews to comply with the current dossier requirements before the start of the MRP procedure.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is medronic acid (also known as methylene diphosphonic, MDP), an established active substance not described in any pharmacopoeia and therefore the MAH has defined his own set of specifications. The active substance is a white powder free of visible contamination. The substance does not show polymorphism.

Manufacture
MDP is prepared in a one step synthesis. Sufficient information has been provided on the synthesis. Since the substance is well known, no information is provided on the structural characteristics. Several degradation products have been described. The MAH has shown by means of batch analysis results (3 batches), with a sufficiently validated GC method, that the described process effectively removes 2-chloropropane. Process validation was not performed since the synthesis is a one step reaction.

Quality control of drug substance
The specifications for MDP are acceptable with regards to related substances, general impurities and quality of the substance. Batch analysis results on 6 batches have been provided. One batch failed to meet the specification for unknown impurities. The MAH stated that this batch was manufactured and tested prior to the update of the specification for the NMR (Nuclear Magnetic Resonance spectroscopy) for each unknown extra peak (limit: NMT 0.1%). The specification was updated and since then, the first three manufactured batches were fully tested and complied with the NMR specification for impurities.

Stability of drug substance
Stability data of six batches have been provided. Three batches were manufactured prior to the initiation of the stability program and therefore have not been tested at all test points. The other three batches have been tested up to 6 months at ambient temperature and humidity conditions for description, loss on drying, pH, assay MDP, assay orthophosphate, purity, known impurities, unknown impurities and bacterial endotoxins. The batches were adequately stored. All values were within specifications. Until a re-test period has been defined, the MAH will fully test all lots of MDP raw material before production of a finished product batch. In the future the MAH will apply for a re-test period by means of a variation.
Medicinal Product

Composition
The product is a kit for the preparation of Technetium ($^{99m}$Tc) medronate Injection, 10 mg medronic acid per vial. The radioisotope is not part of the kit. The medicinal product is a white freeze-dried plug that may break into powder.

The excipients are: stannous chloride dihydrate, p-aminobenzoic acid, hydrochloric acid 1N (pH adjustment), and sodium hydroxide (pH adjustment) and nitrogen (headspace). All excipients comply with their Ph. Eur. Monographs.

Container closure system
The product is packaged in Ph.Eur.* type I clear borosilicate glass vial and grey Ph.Eur. type I butyl rubber stops 20 mm (non-halogenated). The form and dimensions of the vial have been laid down unambiguously by a drawing.

For the 10 ml vial acceptable acceptance criteria are given for description, dimensions, colour, capacity and powdered glass test. For the rubber stopper, acceptance criteria are given for description, dimensions, specific gravity and ash content. For the flip off seal, acceptable acceptance criteria are given for description, dimensions, material and colour.

The rubber stopper also meets the requirements of Ph.Eur. 3.2.9 Rubber closures for containers for aqueous parenteral preparations, for powders and for freeze dried powders, including the self sealing test for closures for multidose containers.

Pharmaceutical development
The manufacturing process for MDP was developed more than 25 years ago. All components are highly soluble chemical entities. The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

Since the product is intended for use with a technetium generator produced by other companies, compatibility studies were carried out. One batch of the product was therefore tested for free pertechnetate (TcO$_4^-$) and reduced hydrolysed pertechnetate (TcO$_2^-$) using generators from two different companies.

The MAH claimed that it is highly likely that all European generators will be identical to the ones studied, as most generators in Europe are derived from the same molybdenum Mo-99 sources as the Canadian and US generators. In accordance with the Note for Guidance on Radiopharmaceuticals, information on the manipulations essential for radiolabelling has been included by the MAH.

Manufacturing process
The process consists of dissolving and combining the components, filling the vials and a lyophilisation procedure. The applicant has adopted a filter sterilisation method and aseptic filling conditions. Steam or dry heat sterilisation were not considered as the product is a lyophilised powder and the stoppers cannot withstand dry heat sterilisation. Irradiation was also not considered as the product is sensitive to free radicals and subsequent darkening of the glass might interfere with assessment of the solution for clarity and particulates. The in-process controls are clearly described and acceptable. They conclude that the submitted documentation, measurements and controls are sufficient to guarantee the sterility of the product. The process has been adequately validated.

Quality control of medicinal product
The product specifications are divided into lyophilized (unreconstituted) product and reconstituted (with Technetium) product. The specifications are in accordance with the Ph. Eur. monograph on Radiopharmaceutical preparations and also based on the monograph of Technetium ($^{99m}$Tc) medronate injection.

The specification for the lyophilized product includes tests for colour, form, appearance, identity, solubility, pH, loss on drying, particulate matter, sterility, bacterial endotoxins, dose uniformity, assay, total tin, oxygen content, identity nitrogen, and orthophosphate.

The specification for the reconstituted product includes tests for radiochemical purity, biological distribution, and radioactivity.
For both presentations, limits in the specification have been justified and are considered appropriate for adequate quality control of the product. The proposed limits for the assay on MDP are normally considered to be too wide. However, they have been accepted previously in several countries, so in this specific case the proposed limits will be accepted based on product history.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from 3 batches from the proposed production site have been provided, demonstrating compliance with the specification.

**Stability tests on the finished product**
A shelf life of 24 months with the storage condition: ‘Do not refrigerate or freeze’ has been granted for the finished product based on submitted stability results of storage for 24 months at normal and 6 months at accelerated conditions. All results complied. The only trend observed was an increase in Loss on Drying.

For the reconstituted product, an in-use period of 12 hours with the storage conditions: ‘Do not store above 25°C. Do not refrigerate or freeze’ has been granted based on the provided results of stability studies.

For the reconstituted product, the MAH has sufficiently demonstrated the stability of the product over the proposed 12 hour period. On the basis of the submitted data the claimed shelf-life after reconstitution of 12 hours can be granted.

**Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies**
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

* Ph.Eur. is an official handbooks (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

### II.2 Non clinical aspects

**Pharmacology**
At the milligram dose of $^{99m}\text{Tc}$-medronate administered for diagnostic procedures, $^{99m}\text{Tc}$-medronate does not exert any pharmacodynamic effects. Therapeutic bisphosphonates (e.g., clodronate and etidronate), given in doses of 5-20 mg/kg, inhibit bone resorption. Their mechanism of action is believed to be threefold: a) a direct effect on the osteoclast activity; b) a direct and indirect effect on the osteoclast recruitment; and c) a shortening of osteoclast survival by apoptosis. Medronate and other bisphosphonates bind strongly to hydroxyapatite crystals at sites of new mineral formation. $^{99m}\text{Tc}$-medronate is thought to separate into its technetium and methylene diphosphonate components in the bone. The technetium is preferentially taken-up by the newly formed osteoid, while the methylene diphosphonate is taken up by the forming mineral.

**Pharmacokinetics**
Studies in several animal models show that $^{99m}\text{Tc}$-medronate accumulates to a much higher degree in bone than in other tissues and to a higher degree in abnormal bone than in normal bone. The distribution and accumulation of diphosphonate complexes is affected by blood flow and extraction efficiency, but is not dose-dependent. Increased blood flow increases the MDP uptake in a non-linear manner, suggesting that bone uptake of $^{99m}\text{Tc}$-medronate is diffusion-limited. MDP is eliminated almost exclusively in urine.

**Toxicology**
A limited number of non-clinical studies have been performed to assess the toxicology of medronate. The non-clinical overview describes old studies. The studies that have been discussed show no toxicological concerns for human safety, as doses at which adverse effects were observed were sufficiently in excess of human therapeutic doses. At the tracer dose of MDP administered for bone scans, the major concern is the radioactive dose of the $^{99m}\text{Tc}$ rather than any potential toxic effect of MDP. Several dosimetry studies have shown the dose of $^{99m}\text{Tc}$ to be safe.
Environmental risk assessment
The receipt, use, transfer and disposal of radiopharmaceuticals are subject to national licensing regulations to minimise the risks to health care professionals, patients, the public and the environment. Draximage MDP is on the Dutch market for many years and comparable products are already on the European market for many years as well. The use of Draximage MDP in stead of other Technetium Tc \(^{99m}\) Medronate products does not contribute to an increase in the exposure of the active drug substance.

II.3 Clinical aspects

Pharmacokinetics
Generally, in the first 3 minutes after injection of technetium (\(^{99m}\)Tc) medronate, there is soft tissue uptake and renal accumulation. With increasing clearance from these compartments, progressive accumulation in the skeletal system is seen, initially in the lumbar vertebrae and the pelvic region. About 50% of the dose injected accumulates in the skeleton. Maximum bone accumulation is reached 1 hour after injection and remains practically constant up to 72 hours. The level of accumulation in the skeletal system depends on the circulation and the extent of regeneration of basic bone material. The circulating unbound complex is eliminated via the kidneys. The peak of activity through the kidneys is reached after approximately 20 minutes. Within 1 hour, with normal renal function, around 32% of the total quantity of unbound complex has undergone glomerular filtration, within 2 hours 47.5% and within 6 hours 60%. The quantity of phosphonate, within the recommended dose range, has no effect on renal excretion.

Pharmacodynamics
At the dose of \(^{99m}\)Tc-medronate administered for diagnostic procedures, medronate does not appear to exert any pharmacodynamic effect.

Clinical Efficacy
As medronate is an old, well established product, the median age of the supporting literature is nearly 2 decades old. While the clinical trial methodology was not as stringent as it is today, the studies as a whole nonetheless provide sufficient evidence of the efficacy of \(^{99m}\)Tc-medronate in the selected indications. These indications are included in practice guidelines issued by each of the European Association of Nuclear Medicine and the Society of Nuclear Medicine in the USA. \(^{99m}\)Tc-medronate has been shown to possess high sensitivity but low specificity for many of the proposed indications. For some indications, additional diagnostic tests might be required in some patients with positive \(^{99m}\)Tc-medronate scans to confirm the diagnosis.

Clinical Safety
Medronate has an acceptable level of safety with the most likely adverse events being rash, nausea and mild anaphylaxis.

Risk management plan
In view of the existing knowledge and experience with the technetium (99mTc) medronate the available data and the known risk benefit profile it is accepted that the MAH will perform the standard Pharmacovigilance activities as described in volume 9 of “The rules governing medicinal products in the European Union”.
Product information

SPC
The SPC is in accordance with the core SPC for these products and therefore considered adequate from a preclinical and clinical point of view.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. First a pilot-test was performed with 5 participants. As a result of this pilot-test many modifications, mostly linguistic, were made to improve the Dutch approved leaflet. With this improved leaflet the readability test was performed.

A first test with the adapted leaflet was performed with 10 participants. This lead to the following major result: more than 90% of the participants was able to locate and understand the information in the leaflet. After the first test several changes were made to the leaflet, mostly linguistical, based on the comments of participants. With this adapted leaflet a second test was performed with 10 participants. Again more than 90% of the participants was able to locate and understand the information in the leaflet. After the second test the Dutch leaflet was adapted again, only to include the changes to the Dutch translation of the QRD template, that was released at that time. This has no consequences for the English translation.

There were sufficient questions about the critical sections. The questions covered the following areas well: traceability, comprehensibility and applicability. The final conclusion of the test is clear, concise and clearly presented. The patient information leaflet has been adapted sufficiently taking into account the results of the tests.
III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The use of this product for the applied applications is well-established for over forty years. The clinical efficacy of DraxImage MAA for the indications stated in the SPC may be concluded beyond any reasonable doubt. The safety aspects are well known and adverse events are known to occur rarely. In Europe a core SPC has been approved taking into account all available information. Furthermore, no real new insights have arisen into the clinical and preclinical field since the nineties, and, to our knowledge, many comparable products are registered in Europe based on the findings of the same ARPE expert report.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates. The SPC is in accordance with the core SPC for these products and therefore considered adequate from a preclinical and clinical point of view.

The opinion of the MEB was discussed in the Board meeting of 15 January 2004. The MEB, on the basis of the data submitted, considered that DraxImage MDP, powder for solution for injection 10 mg demonstrated adequate evidence of efficacy for the approved indication(s) as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation. The date of authorisation was on 29 March 2006 in the Netherlands.

The mutual recognition procedure was started on 20 October 2007. There was no discussion in the CMD(h). Agreement between Member States was reached during a written procedure. The mutual recognition procedure was finished on 18 January 2008. The other Member States mutually recognised the Dutch evaluation for the marketing authorisation.

The first PSUR will cover the period from March 2009 to March 2010, after which the PSUR submission cycle is 1 year.

The date for the first renewal will be: 29 November 2010.

The following post-approval commitments have been made during the procedure:

Clinical aspects
- On request of some CMS’s, the MAH has committed to submit a variation to update the SPC of this product according to the updated version of the core SPC for medronic acid as soon as this core SPC is published by the corresponding EMEA group.

Pharmacovigilance system
- The MAH has committed to establish SOPs covering the activities “activities and back-up procedure for the QPPV”, “detection of duplicates”, “electronic reporting”, “monitoring and signal detection”, “responding to requests for information from regulatory authorities”, “handling of USRs and other safety variations”, “meeting commitments to competent authorities”, “management and use of databases”, and “archiving” and to implement these SOP by September 2008, before launch of the product. This commitment has been fulfilled by post-approval variation NL/H/0962/001/II/001. See “Steps taken after finalisation of the initial procedure” table on page 10.
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ASMF</td>
<td>Active Substance Master File</td>
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<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical classification</td>
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<td>AUC</td>
<td>Area Under the Curve</td>
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<td>BP</td>
<td>British Pharmacopoeia</td>
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<td>CEP</td>
<td>Certificate of Suitability to the monographs of the European Pharmacopoeia</td>
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<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<td>CI</td>
<td>Confidence Interval</td>
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<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximum plasma concentration</td>
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<td>CMD(h)</td>
<td>Coordination group for Mutual recognition and Decentralised procedure for human medicinal products</td>
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<td>CV</td>
<td>Coefficient of Variation</td>
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<td>EDMF</td>
<td>European Drug Master File</td>
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<td>European Directorate for the Quality of Medicines</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>Good Laboratory Practice</td>
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<td>International Conference of Harmonisation</td>
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<td>MAH</td>
<td>Marketing Authorisation Holder</td>
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<td>MEB</td>
<td>Medicines Evaluation Board in the Netherlands</td>
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<td>NMR</td>
<td>Nuclear Magnetic Resonance (spectroscopy)</td>
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<tr>
<td>OTC</td>
<td>Over The Counter (to be supplied without prescription)</td>
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<td>PAR</td>
<td>Public Assessment Report</td>
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<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<td>PIL</td>
<td>Package Leaflet</td>
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<td>PSUR</td>
<td>Periodic Safety Update Report</td>
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<td>Standard Deviation</td>
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<td>SPC</td>
<td>Summary of Product Characteristics</td>
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<td>t&lt;sub&gt;½&lt;/sub&gt;</td>
<td>Half-life</td>
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<tr>
<td>t&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Time for maximum concentration</td>
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<td>TSE</td>
<td>Transmissible Spongiform Encephalopathy</td>
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<td>USP</td>
<td>Pharmacopoeia in the United States</td>
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### STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

<table>
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<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Type of modification</th>
<th>Date of start of the procedure</th>
<th>Date of end of the procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached</th>
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<td>Change to the Pharmacovigilance (PV) System. Change to the EU Qualified Person (QP) responsible for Pharmacovigilance.</td>
<td>NL/H/0962/001/I/001</td>
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<td>15-10-2009</td>
<td>14-12-2009</td>
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<td>22-1-2010</td>
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