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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Veterinary Use

# European public MRL assessment report (EPMAR)

## Prednisolone (*Equidae*)

On 2 May 2013 the European Commission adopted a Regulation[1] establishing maximum residue limits for prednisolone in *equidae*, valid throughout the European Union. These maximum residue limits were based on the favourable opinion and the assessment report adopted by the Committee for Medicinal Products for Veterinary Use.

Maximum residue limits had previously been established for prednisolone (as free alcohol) in bovine species. Two independent applications for the extension of maximum residue limits to equidae were received by the European Medicines Agency on 28 and 29 September 2011, one from Cygnus BV and the other from Le Vet B.V.

Prednisolone is intended for use in horses for the relief of recurrent airway obstruction and inflammation in heaves-affected animals.

Based on the data in the dossiers, the Committee for Medicinal Products for Veterinary Use recommended, on 8 March 2012, the extension of maximum residue limits for prednisolone to *equidae*.

On 23 March 2012 Le Vet informed the European Medicines Agency that it intended to request a re-examination of the CVMP opinion and the grounds for the re-examination were submitted on 19 April 2012. The Committee for Medicinal Products for Veterinary Use adopted its final opinion on 14 June 2012.

Subsequently the Commission recommended, on 20 March 2013, that maximum residue limits in *equidae* be established. This recommendation was confirmed on 10 April 2013 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 2 May 2013.

[1] Commission Implementing Regulation (EU) No 406/2013, O.J. L 121, of 3 May 2013

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# European public MRL assessment report (EPMAR)

Prednisolone (*Equidae*)

## Summary of the scientific discussion for the establishment of MRLs

| | |
|---|---|
| Substance name: | Prednisolone |
| Therapeutic class: | Corticoids/Glucocorticoids |
| Procedure number: | EU/11/196/CYG and EU/11/197/LEV |
| Applicant: | Cygnus BV and Le Vet B.V. |
| Target species: | *Equidae* |
| Intended therapeutic indication: | Relief of recurrent airway obstruction and inflammation in heaves-affected horses |
| Route(s) of administration: | Oral |

## 1. Introduction

Prednisolone is a synthetic glucocorticosteroid. In veterinary medicine, prednisolone (as the free alcohol) is included as an ingredient in a number of antibiotic preparations, which are indicated for intramammary administration for the treatment of bovine mastitis. The usual dose corresponds to 10 mg prednisolone per infected quarter. Treatment may be repeated at 12-hour intervals for a maximum of 3 treatments.

Prednisolone was previously assessed by the CVMP and a pharmacological ADI of 0.0002 mg/kg bw (i.e. 0.012 mg/person) was established.

Currently, prednisolone is included in Commission Regulation (EU) No 37/2010 of 22 December 2009 in accordance with the following table:

| Pharmacologically active substance | Marker residue | Animal species | MRLs | Target tissues | Other provisions | Therapeutic classification |
|---|---|---|---|---|---|---|
| Prednisolone | Prednisolone | Bovine | 4 µg/kg<br>4 µg/kg<br>10 µg/kg<br>10 µg/kg<br>6 µg/kg | Muscle<br>Fat<br>Liver<br>Kidney<br>Milk | NO ENTRY | Corticoids/ Glucocorticoids |

On 28 September 2011 Cygnus BV submitted to the European Medicines Agency an application for the extension of maximum residue limits for prednisolone to *Equidae*. On 29 September Le Vet BV submitted to the European Medicines Agency an application for the extension of maximum residue limits for prednisolone to *Equidae.*

The intended use in *Equidae* is for relief of recurrent airway obstruction and inflammation in heaves-affected horses. For oral administration, the proposed minimum dose is of 1 mg prednisolone/kg bw/day which might be repeated once at 24 hour intervals during 10 consecutive days.

# 2. Scientific risk assessment

The scientific risk assessment for the extension of maximum residue limits for prednisolone to *Equidae* takes into consideration the data submitted by both companies within their respective applications.

## *2.1. Safety assessment*

The CVMP previously assessed the consumer safety of prednisolone and a pharmacological ADI of 0.0002 mg/kg bw (i.e. 0.012 mg/person) was established by applying a safety factor of 100 to the NOEL of 20 µg/kg bw/day which was established for induction of tyrosine aminotransferase activity in rats. Therefore, no further assessment regarding the consumer safety of the substance is required for the purpose of this extension application.

## *2.2. Residues assessment*

### 2.2.1. Pharmacokinetics in target species

A pharmacokinetic study was conducted to determine prednisolone concentrations in plasma of 12 healthy horses (377 to 693 kg) following oral administration of a prednisolone formulation at a target dose of 1 mg prednisolone/kg bw, once daily for 14 days. Blood samples were collected just before and then frequently after the 1$^{st}$, 7$^{th}$, 14$^{th}$ administrations. Samples were collected after 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 10, 16 and 24 hours after administration and at 34, 48 and 72 hours after the last administration. A steady state had been reached after 7$^{th}$ administration and the $C_{ss(min)}$ (minimum concentration during any dosing interval at steady state) was calculated as 0.4 ng/ml with $C_{ss(max)}$ (maximum concentration during any dosing interval at steady state) being 284 ng/ml. The $T_{max}$ was 3.4 ± 3.5, 2.3 ± 3.0 and 1.9 ± 2.7 hours with the highest concentrations of ($C_{max}$) 189 ± 119, 284 ± 185 and 239 ± 148 ng/ml after the 1$^{st}$, 7$^{th}$ and 14$^{th}$ administrations respectively. The elimination half-life ($t_{½}$) was between 3.0 and 3.2 hours with the area under the concentration-time curve ($AUC_{\infty}$) ranging between 1030 and 932 ng.hour/ml.

In a crossover study, 5 horses were given treatments consisting of prednisone tablets, prednisone liquid, and intravenous prednisolone sodium succinate (positive control). Blood samples were taken before drug administration and at selected time points during a 24-hour period. Both prednisolone tablets and liquid were absorbed rapidly, with prednisolone detectable in serum within 15 minutes of administration and with peak concentrations occurring within 45 minutes. Small amounts of prednisone were detected in the serum samples after administration of both prednisone tablets and liquid. Prednisolone was not detected in serum samples after administration of prednisone liquid and was detected in serum samples from only one horse after administration of prednisone tablets. The mean bioavailability for the oral prednisolone tablets and oral prednisolone liquid following administration of 2.2 mg prednisolone/kg bw dose were 65% (± 5.1) and 56% (± 14.4) respectively. The mean $C_{max}$ values were 622 ± 138.7 and 311 ± 46.0 ng/ml and these concentrations were reached after ($T_{max}$) 45 minutes.

Pharmacokinetics of dexamethasone and prednisolone were studied in 6 horses given dexamethasone alcohol (intravenously or intramuscularly) or dexamethasone 21-isonicotinate (intravenously or intramuscularly, 50 µg/kg bw), prednisolone 21-sodium succinate (intravenously or intramuscularly, 0.6 mg/kg bw), or prednisolone acetate (intramuscularly, 0.6 mg/kg bw). After intramuscular administration, there was rapid prednisolone absorption. The half-life of absorption was short (7.15 ± 10.7 minutes) and bioavailability was 91.9 ± 7.98%. The apparent $t_{1/2}$ of elimination was slightly longer than after intravenous administration (132.9 ± 25.63 minutes).

The plasma concentration of prednisolone in equine blood following oral administration of tablets and gel was studied. The results were compared to the intramuscular injection of prednisolone suspension and for each method of application the pharmacokinetic parameters were calculated based on the plasma concentrations. Prednisolone was administered at 0.5, 1.0 and 2 mg/kg bw. The plasma concentrations of prednisolone following intramuscular injection were dose-dependent with average maximum concentrations between 79 and 172 ng/ml which were reached after 0.4 to 3.9 hours. The mean clearance was 5 to 9 ml/min and the half-life was about 14 hours. After intramuscular injection of 1 mg/kg prednisolone-acetate to eight horses prednisolone was detectable in the plasma for 10 days. In five horses the substance could be found even after 12 days. The mean maximum plasma concentration of 52 ng/ml was reached after 14.5 hours. The clearance was on average 5 ml/min and the prednisolone half-life in plasma was 39 hours. After oral administration of either tablets or gel prednisolone was detectable in the plasma in dose-dependent concentrations. The average maximum concentrations were 94 to 327 ng/ml (tablets) and 54 to 243 ng/ml (gel). The average maximum plasma concentrations were reached 0.5 to 0.9 hours after tablet- and 1.7 to 3.6 hours after gel-administration. The mean prednisolone half-life in plasma following administration of tablets was 2.6 hours; the clearance increased from 21 to 28 ml/min dependent on the dosage. After treatment with gel the prednisolone half-life in plasma varied between 4.8 and 5.5 hours, the clearance was 22 to 26 ml/min.

A pharmacokinetic study was performed in six horses which were administered prednisolone via the intravenous route and blood samples collected for 3.5 days. Following a wash out period of 10 days, 4 daily doses of 1 mg prednisolone/kg bw/day were administered orally. Baseline samples were taken 2 days prior to oral administration. Blood samples were then collected for 3 days. Urine samples were also taken 5 and 7 days after the last administration. Absorption after oral administration was fast and calculated to be 44%. Elimination $t_{1/2}$ following oral administration was 7.25 hours and following intravenous administration was 3.5 hours. The highest concentration following oral administration ($C_{max}$) was 0.36 µg/ml and it was reached after 1.46 hours ($T_{max}$). The AUC was 2.72 and 1.33 µg/ml/hr following intravenous and oral administrations respectively.

### 2.2.2. Residue depletion studies

On one study, twenty horses (12 horses in one study and 8 horses in a second study) were administered oral formulation of prednisolone at a target dose of 1 mg prednisolone/kg bw, once daily for 14 days. The animals were slaughtered at 1, 3, 7, 14 and 28 days (7, 14 and 28 days in the first study and 1 and 3 days in the second study) after last administration. Prednisolone tissue levels were determined using LC-MS/MS in liver, kidney, muscle and fat tissues. The highest prednisolone residue levels were found at day 1 in all tissues and residues in liver, kidney, muscle and fat ranged from 4.4 to 6 µg/kg; 4.9 to 31.2 µg/kg; 2.4 to 3.8 µg/kg and 8.5 to 18.3 µg/kg respectively. The levels then depleted to between 2.4 and 4.2 µg/kg in liver, below 1 and 2.3 µg/kg for kidney, 1.6 and 4.9 µg/kg for muscle and 0.9 and 5.1 µg/kg for fat 3 days after the last administration.

In another study, sixteen clinically healthy horses (440 to 650 kg) were administered oral prednisolone capsules at a target dose rate of 1 mg prednisolone/kg bw/day for 14 days. The animals were slaughtered at 1, 2, 3 and 4 days after last administration and prednisolone tissue levels were determined using LC-MS in liver, kidney, muscle and fat tissues. The highest prednisolone residue levels were found at day 1 in all tissues and residues in liver, kidney, muscle and fat ranged from 4.8 to 9.8 µg/kg; 12.5 to 19.2 µg/kg; 3.2 to 6.4 µg/kg and 3.8 to 6.4 µg/kg respectively.

**Selection of marker residue and ratio of marker to total residues**

The CVMP previously concluded that prednisolone accounted for all the residues with corticosteroid activity. Therefore, similarly to what was concluded with regard to the evaluation concerning bovine species, prednisolone was retained as the marker residue and the ratio of marker to total residues set at 1.

### 2.2.3. Monitoring or exposure data

No monitoring or exposure data other than that described elsewhere in this report were available.

### 2.2.4. Analytical method for monitoring of residues

An analytical method for the determination of prednisolone residues in horse tissue is available. Prednisolone was extracted from tissues by liquid/liquid extraction and identification was by LC-MS/MS. The limit of quantification was 1 µg/kg for liver and kidneys and 0.4 µg/kg for muscle and fat. Specificity in the presence of analogous substances was not demonstrated.

A second analytical method for the determination of prednisolone residues in horse tissue was available. Following a liquid/liquid extraction separation was by LC with MS detection. The limit of quantification was 2 µg/kg for all tissues (liver, kidneys, muscle and fat). The analytical method can be considered validated in line with the guideline on safety and residue data requirements for veterinary medicinal products intended for minor uses or minor species (EMEA/CVMP/SWP/66781/2005).

The relevant EU reference laboratory was consulted on the analytical methods, their assessment of the analytical methods is supportive of the above conclusions.

### 2.2.5. Findings of EU or international scientific bodies

No evaluations by the FAO/WHO Joint Expert Report of Feed Additives (JECFA) and other international committees were available.

## 3. Risk management considerations

### *3.1. Potential effects on the microorganisms used for industrial food processing*

Microbiological effects are not expected for this type of substance therefore no data were required.

### *3.2. Other relevant risk management considerations for the establishment of maximum residue limits*

None.

### *3.3. Elaboration of MRLs*

Following the tissue residue depletion studies in horses, the following recommendation for the establishment of MRLs for horses can be made: muscle 4 µg/kg, fat 4 µg/kg, liver 6 µg/kg and kidney: 15 µg/kg.

The CVMP explored the option of establishing the same MRLs as for bovine tissues, but noted that the bovine MRLs were based only on data following intramammary administration while the data available

for horses followed oral administration which is the intended use of the substance in this animal species.

**Calculation of theoretical intake of residues**

The calculation below is based on residue levels at a time where the theroretical maximum daily intake (TMDI) falls below the ADI (2 days) and includes the intake of residues from milk.

| Tissue | Food basket (kg) | MRLs (µg/kg) | TMDI (µg) | % ADI |
|---|---|---|---|---|
| Muscle | 0.3 | 4 | 1.2 | 10 |
| Fat | 0.05 | 4 | 0.2 | 1.67 |
| Liver | 0.1 | 6 | 0.6 | 5 |
| Kidney | 0.05 | 15 | 0.75 | 6.25 |
| *Milk* | *1.5* | *6* | *9* | *75* |
| | | Total | 11.75 | 97.9 |

Based on the recommended MRLs the theoretical daily intake of residues from horse tissues represents 23% of the ADI (12 µg /person). Considering in addition the intake of residues from milk the theoretical daily intake represents 98% of the ADI.

## *3.4. Considerations on possible extrapolation of MRLs*

In line with Article 5 of Regulation (EU) No 470/2009 the CVMP considered the possibility of extrapolating the maximum residue limits established for prednisolone to other food producing species and food commodities. The Committee noted that the recommendation for the establishment of MRLs for cattle were based on data from intramammary administration only. There are no data from species other than the horse following oral administration. Taking into account the current scientific knowledge the recommendations on extrapolation are justified as follows:

| Animal species/ food commodities | Extrapolation possible (Yes/No) | Justification |
|---|---|---|
| Pigs | No | No pharmacokinetic or residue depletion data were available for pigs. As pigs meat is consumed on a regular basis and in large quantities across the EU, species specific data are considered necessary in order to quantify the possible impact on consumer safety of exposure to residues.<br>No analytical method for monitoring of residues in pig tissues was available for evaluation. |
| Chicken (including eggs) | No | No pharmacokinetic or residue depletion data were available for chicken. As chicken meat is consumed on a regular basis and in large quantities across the EU, species specific data are considered necessary in order to quantify the possible impact on consumer safety of exposure to residues.<br>No analytical method for monitoring of residues in chicken tissues and eggs was available for evaluation. |

| | | |
|---|---|---|
| Sheep (including milk) | No | No pharmacokinetic or residue depletion data were available for sheep. As sheep meat is consumed on a regular basis and in large quantities across the EU, species specific data are considered necessary in order to quantify the possible impact on consumer safety of exposure to residues.<br><br>No analytical method for monitoring of residues in sheep tissues and milk was available for evaluation. |
| Goats (including milk) | No | No pharmacokinetic or residue depletion data were available for goats. Species specific metabolism and residue data are needed in order to draw conclusions on safe MRL levels.<br><br>No data are available to demonstrate that the analytical method for monitoring of residues is applicable for monitoring of residues in goats tissues or milk. |
| Rabbits | No | No pharmacokinetic or residue depletion data were available for rabbits. Species specific metabolism and residue data are needed in order to draw conclusions on safe MRL levels.<br><br>No data are available to demonstrate that the analytical method for monitoring of residues is applicable for monitoring of residues in rabbits tissues. |
| Fin fish | No | Metabolism in fin fish is generally less complicated than in horses. Consequently, if the parent compound is the marker residue in bovines it can be assumed that the parent compound would also be the suitable marker residue in fish meat. However, no analytical method for monitoring of residues in fin fish was available for evaluation. |
| Honey | No | Residue depletion in honey does not occur through metabolism and therefore conclusion drawn from data in other food products cannot be extrapolated to honey. Honey specific data are required in order to allow adequate evaluation of the risk to consumer safety posed by residues in honey.<br><br>No data are available to demonstrate that the analytical method for monitoring of residues is applicable for monitoring of residues in honey. |

## *3.5. Conclusions and recommendation for the establishment of maximum residue limits*

Having considered that:

- the pharmacological ADI of 0.2 µg/kg bw (i.e. 12 µg/person) was established as the overall ADI for prednisolone,
- the parent compound prednisolone was retained as the marker residue,

- the ratio of marker to total residues of 1 was set for all tissues as the marker residue accounted for all the residues with corticosteroid activity,
- a validated analytical method for the monitoring of residues of prednisolone in edible horse tissues (muscle, fat, liver, and kidney ) is available,

the Committee recommends the extension of maximum residue limits for prednisolone in horses in accordance as follows:

| Pharmacologically active substance | Marker residue | Animal species | MRLs | Target tissues | Other provisions | Therapeutic classification |
|---|---|---|---|---|---|---|
| Prednisolone | Prednisolone | *Equidae* | 4 µg/kg<br>4 µg/kg<br>6 µg/kg<br>15 µg/kg | Muscle<br>Fat<br>Liver<br>Kidney | NO ENTRY | Corticoids/ Glucocorticoids |

Based on the recommended MRLs and the MRLs established for milk the theoretical daily intake of residues from horse tissues represents 98% of the ADI (12 µg /person).

# 4. Re-examination of the CVMP opinion of 8 March 2012

## *4.1. Grounds for re-examination*

The request for re-examination indicated that the CVMP recommendation did not consider all the available data. The request for the re-examination as provided by the applicant is summarised below:

1. MRLs of 3, 16, 11 and 7 µg/kg for muscle, fat, liver and kidney respectively would better reflect the depletion profile.
2. Although the applicant is not aware of data on day 2, 3 and 4 of the other study he can deduce from his own data that the depletion of prednisolone in the matrices liver and fat is much slower than the depletion in kidney. Normally those “withdrawal time” determining matrices should have a higher MRL than the muscle and kidney.
3. The residue depletion data (day 7 to 28) show highly variable results and occasional outlying values, well above the MRLs suggested for liver and fat. It cannot be assumed that these outlying values are formulation related and therefore these data should be mentioned in the summary report and also included in the elaboration of the MRL definition.
4. The MRLs suggested will result in extremely long withdrawal time determinations for the Applicants formulation or, in a worst-case scenario, in not being able to set a withdrawal time at all.
5. Applying the MRLs suggested will in practice result in (frequent) suspected withdrawal time violations.
6. The fact that the above MRLs utilise 101% of the ADI should not be considered a problem given that in previous MRL evaluations, MRL values which utilised more than 100% of the ADI were allowed,
7. This MRL applications concern a MUMS application, i.e. hardly used (only in patients) and therefore treated animals are not likely to be used for human consumption after treatment.

## *4.2. Overall conclusion on grounds for re-examination*

When re-examining the data the CVMP considered that in addition to the residue levels reported in section 2.2.2. (second paragraph), the following information should be added for completion of the report "*At day 2 residues ranged from below the limit of quantification (<LOQ) to 3.8 µg/kg in liver; 3.1 to 7.3 µg/kg in kidney; below the limit of quantification to 2.2 µg/kg in muscle and <LOQ to 3.7 µg/kg in fat. At day 3 residues ranged from <LOQ to 3.6 µg/kg in liver and were <LOQ in all other tissues. Residues were below the limit of quantification (2 µg/kg) in all tissues after 4 days.*"

The proposed MRLs of 3 µg/kg for muscle, 16 µg/kg for fat, 11 µg/kg for liver and 7 µg/kg for kidney in the request for re-examnination cannot be accepted for the following reasons:

1. MRLs of 3, 16, 11 and 7 µg/kg for muscle, fat, liver and kidney respectively do not follow the tissue distribution and they do not take into account the 1$^{st}$ time point at which the theoretical maximum daily intake would be below the ADI. There is no justification for an MRL for fat as high as 16 µg/kg since at day 3 the maximum fat value was about 5 µg/kg. Furthermore, there is no justification for an MRL for liver as high as 11 µg/kg; also MRLs should be established according to the tissue distribution and may not be recommended based on extreme values. While faster depletion was seen in kidney, this was also the tissue in which the highest concentration was observed at day 1; therefore, together with the results of the other applicant where high residue values where observed, it seems logical to assign a high MRL value for this tissue. In addition, these proposed MRLs would result in the ADI being exceeded.
2. MRLs are based on tissue distribution at a time where the theoretical maximum daily intake falls below the ADI. The CVMP's original proposal followed tissue distribution but given the higher residues observed in fat in one of the studies evaluated (at day 1), it is possible to increase the fat MRL to 8 µg/kg whilst not deviating from the totality of data on tissue distribution and ensuring the theoretical maximum daily intake remained below the ADI.
3. Although it may not be assumed that the outlying values were formulation related, there could have been other factors that produced the results. In any case, when establishing MRLs, all available data is considered and a decision made based on the totality of the available data.
4. The MRLs proposed by CVMP, including the revised value for fat (8 µg/kg), are based on all the data submitted and the Committee believes that a practical meat withdrawal period for prednisolone is possible.
5. Once MRLs are established and adequate withdrawal periods set, it is the responsibility of those using the veterinary medicinal product to ensure that withdrawal periods are respected.
6. The theoretical maximum daily intake following establishment of MRLs should not exceed the ADI.
7. Horses are considered as minor species and MRLs are established in accordance with the current guidance which already takes into account the possible reduced exposure of consumers to residues.

The MRLs recommended for horses, including the increased fat MRL, i.e 4 µg/kg for muscle, 8 µg/kg for fat, 6 µg/kg for liver and 15 µg/kg for kidney, represent 24.6% of the ADI. The MRLs previously established for cattle tissues represent 24% of the ADI, while the MRLs recommended for cattle milk represent 75% of the ADI. Therefore, the worst case theoretical maximum daily intake arises from the ingestion of horse tissues (24.6%) and bovine milk (75%). This represents 99.6% of the ADI.

# 5. Conclusions and recommendation for the establishment of maximum residue limits following re-examination

Having considered that:

- the pharmacological ADI of 0.2 µg/kg bw (i.e. 12 µg/person) was established as the overall ADI for prednisolone,
- the parent compound prednisolone was retained as the marker residue,
- the ratio of marker to total residues of 1 was set for all tissues as the marker residue accounted for all the residues with corticosteroid activity,
- a validated analytical method for the monitoring of residues of prednisolone in edible horse tissues (muscle, fat, liver, and kidney) is available.

Having considered the arguments raised in the detailed grounds for re-examination and taking into account all the supporting data on safety of residues, the Committee recommends the extension of maximum residue limits for prednisolone in *Equidae* as follows:

| Pharmacologically active substance | Marker residue | Animal species | MRLs | Target tissues | Other provisions | Therapeutic classification |
|---|---|---|---|---|---|---|
| Prednisolone | Prednisolone | *Equidae* | 4 µg/kg<br>8 µg/kg<br>6 µg/kg<br>15 µg/kg | Muscle<br>Fat<br>Liver<br>Kidney | NO ENTRY | Corticoids/ Glucocorticoids |

Based on the recommended MRLs and the MRLs established for milk the theoretical daily intake of residues from horse tissues represents 99.6 % of the ADI (12 µg /person).

# 6. Background information on the procedure

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| Submission of the dossier (EU/11/196/CYG): | 28 September 2011 |
| Steps taken for assessment of the substance | |
| Application validated: | 12 October 2011 |
| Clock started: | 13 October 2011 |
| Submission of the dossier (EU/11/197/LEV): | 29 September 2011 |
| Steps taken for assessment of the substance | |
| Application validated: | 12 October 2011 |
| Clock started: | 13 October 2011 |
| CVMP opinion adopted: | 8 March 2012 |
| Submission of grounds for examination | 19 April 2012 |
| Adoption of final opinion | 14 June 2012 |