rvp\I
case number 239877
cause-list number: KG ZA 05-354
date of judgment: 25 April 2005 (by anticipation)

**DISTRICT COURT OF THE HAGUE**
**Civil Law Section • Preliminary Relief Judge**

Judgment in preliminary relief proceedings[1] in the matter of the aforementioned case and cause-list number between:

**the legal entity under foreign law**
**MSD OVERSEAS MANUFACTURING**,
having its registered office at Pembroke, Bermuda,
the claimant,
local counsel: *mr*. P.J.M. von Schmidt auf Altenstadt,
attorney: *mr.* L. Oosting of Amsterdam,

and:

1. **the private company with limited liability**
**TEVA PHARMACEUTICALS EUROPE B.V.**,
having its registered office in Mijdrecht, the Netherlands,
2. **the private company with limited liability**
**TEVA PHARMA B.V.**,
having its registered office in Mijdrecht, the Netherlands,
3. **the private company with limited liability**
**PHARMACHEMIE**,
having its registered office in Haarlem, the Netherlands,
defendants,
local counsel: *mr.* M.A.A. van Wijngaarden

The parties are hereinafter (also in the operative part hereof ) referred to as 'Merck' and 'Teva'.

**CONSIDERATIONS REGARDING THE COURSE OF THE PROCEEDINGS**

Merck has summoned Teva to appear at preliminary relief proceedings on 14 April 2005, pursuant to the order in that respect. During the hearing, *mr*. Oosting explained the statements of Merck based on pleading notes and exhibits, assisted by Dr. H.J.R. de Boer, patent attorney. Teva has put forward a defence via *mr.* Van Wijngaarden at the hearing referred to, also based on pleading notes and exhibits and assisted by Dr. Ir. H.W. Prins, patent attorney. Thereupon judgment was requested on the basis of the documents, including the aforementioned pleading notes and exhibits, which judgment is to be decided upon today.

**GROUNDS**

1. Basic premises

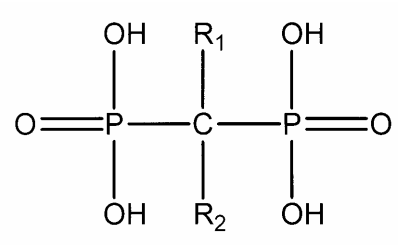
1.1 In the preliminary relief proceedings the following can be assumed.

1.2 Upon transfer, Merck owned Dutch patent 192562 (hereafter the Patent or NL '562) granted on 3 October 1997 upon an application on 15 April 1983 invoking a priority

[1] Also known as summary proceedings

right from 15 April 1982 to a *pharmaceutical preparation that contains a $NH_2$-$(CH_2)_3$-$C(PO_3H_2)_2OH$ compound.*

1.3 The compound referred to belongs to the group of bisphosphonates with the general structural formula:




Bisphosphonates have two C-P compounds and an inhibitory effect on bone resorption. Bones are replaced in a continuous process. The removal of old bone is called resorption and the formation of new bone is called mineralisation. Normally, the two processes are in equilibrium. In the case of bone diseases this equilibrium is disrupted and on balance more resorption than mineralisation occurs. Osteoporosis is a well-known bone disease that occurs relatively frequently among women after menopause. Another bone disease that is treated with bisphosphonates is Paget's disease.
The compound, which forms the core of the patent, has a carbon chain of four C atoms with a hydroxyl group on the 1 position and an amino group at the end of the carbon chain (thus, $R_1 = (CH_2)_3$-$NH_2$ and $R_2$ = OH) and, to use the language used by the parties, it is specified as alendronate or the C-4 compound (4-amino-1, hydroxybutane-1, 1-bisphosphonic acid or the salt from it). Other related substances known on the priority date are etidronate, a C-2 compound without an amino group (in the English scientific literature also indicated with the abbreviation EHDP), clodronate, with a C-$Cl_2$ (also known as $Cl_2$MDP, where $R_1$= $R_2$=Cl), likewise without an amino group at the end of the chain, pamidronate, a C-3 compound with a $NH_2$ group at the end of the chain, just like alendronate, and an OH group at the 1 position, also described as AHPDP, as well as neridronate, a C-6 compound with an OH group at 1 and a $NH_2$ group at 6. On the priority date a C-5 compound was also known for which no current derivative name was used.
The patent was granted under the Dutch Patent Act of 1910 and thus concerns a preliminary investigated patent. It was initially refused by the Application Section of the Patent Office by virtue of a decision on 10 November 1987, which was reversed by a decision on 28 February 1997 (sent on 3 March 1997) after proceedings before the Board of Appeal. Subsequently, the patent was granted on 3 October 1997 after the last changes suggested by the Board were implemented. The patent expired on 15 April 2003, but Merck still claims rights under this patent because of a supplementary protection certificate based on NL '562, which was granted to Merck under number 970038 and is valid up to and including 14 April 2008. This supplementary protection certificate was issued to Merck for: *alendronic acid, if so desired in the form of a (...) salt with an alkali metal, an organic base or a basic amino acid in the form of a hydrate, in particular Natrii Alendronas Trihydric.*

1.4 Thus, the claims of NL '562 are:

*1. A pharmaceutical preparation that contains a $NH_2$-$(CH_2)_3$-$C(PO_3H_2)_2OH$ compound, characterized in that it is a preparation suitable for the treatment of bone diseases, in which the 4-amino-1-hydroxy butane-1, 1-bisphonic acid is present as such or in the form of a salt with an alkali metal, an organic base or a basic amino acid, on the understanding that it is the only pharmaceutically*

*active substance in the preparation if the 4-amino-1-hydroxy butane-1, 1-bisphonic acid is not present in the form of a salt.*

2. *A pharmaceutical preparation according to claim1, characterized in that the preparation in a solid form is meant for oral administration.*

1.5 In 2002 Merck instituted preliminary relief proceedings against Teva over an impending infringement of the patent. The case was not seen through at that time, in short because Teva undertook not to market a generic alendronate against bone disease for the time being, and, if it would intend to do so in future, to announce such an intention six weeks in advance. In the beginning of March 2005, Teva, in accordance with what was agreed in 2002, announced that it currently has the intention to enter the market with a generic alendronate.

1.6 Teva is of the opinion that NL '562 isinvalid, just like the supplementary protection certificate issued on the basis of that patent.

1.7 The English judge has deemed the British sister patent of NL '562 (at least in the eyes of Teva), null and void, both in the first instance and on appeal.

1.8 One day before the hearing of the preliminary relief proceedings, on 13 April 2005, Teva instituted proceedings on the merits at the District Court of The Hague with the revocation of the supplementary protection certificate as the reason for the proceedings, inter alia because of the invalidity of NL '562.

## 2. The dispute

2.1 Merck requests an infringement injunction with ancillary claims, stating that Teva is threatening to infringe upon its rights under the supplementary protection certificate, currently referred to in the proceedings.

2.2 During these proceedings Teva, when requested, specifically does not expand on the statement that the intended generic alendronate preparation would infringe upon the claims of the patent via the route of the supplementary protection certificate. Thus, it exclusively puts forward a defence of invalidity with regard to both NL '562 and – partly on other grounds – the supplementary protection certificate. Its defence will as far as possible be discussed during the assessment.

## 3. Assessment of the dispute

3.1 The requested relief of Merck cannot be allowed, because, as a provisional opinion[2], there is a realistic chance that the patent will be considered null and void during the proceedings on the merits, so that Merck, on this ground alone, cannot assert any claim against Teva under the supplementary protection certificate referred to above. The following serves as a reason in this regard.

3.2 As such, the statement by Merck that in preliminary relief proceedings the judge is not deemed to repeat the proceedings before the Board of Appeal is accurate. In the proceedings at hand Teva, in support of its defence that the patent must fail the inventive step test, invoked new documents, of which it has currently become plausible in preliminary relief proceedings that – different from what was argued by Merck during the oral hearing – they have not been (to a sufficiently knowable degree, at least one that can be considered relevant) discussed during the proceedings at the Board of

[2] Here, and throughout the judgment, the judge shows that his assessment and decision(s) have a provisional nature.

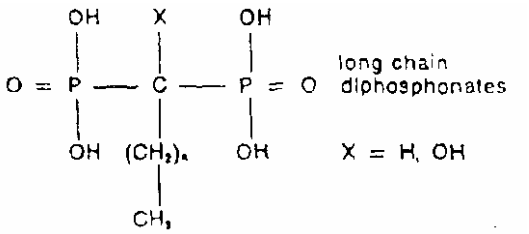
Appeal. As a provisional opinion, these documents, particularly the publications of Fleisch and Felix, to be more closely indicated hereafter, are in the soon to be indicated context damaging to inventive step.

3.3 One of the new documents referred to in 3.2 is a review by Fleisch, a well-known researcher in the field of bisphosphonates, in the *British Journal of Clinical Practice* in 1981, as a result of a symposium about bisphosphonates (also referred to as diphosphonates) and Paget's disease, entitled *Diphosphonates: History and mechanisms of action*. The article or what is disclosed therein is not (to the full extent) disclosed in the description of the patent and at the Board of Appeal it also did not play any knowable role. It appears, inter alia from the article, that the clinical application of several bisphosphonates was known for the treatment of bone diseases on the priority date. According to Fleisch, the C-3 compound, pamidronate, was the most effective against bone diseases. As far as it is currently of interest, it specifically relates to the decrease of bone resorption. According to this review, the skilled man has known the following already since 1968 :

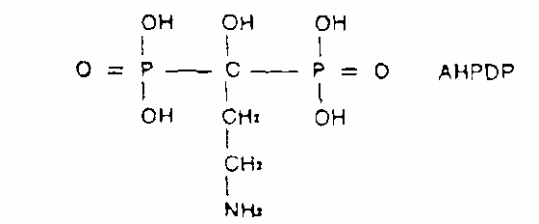
> *In 1968 (...) we reported the first results: besides inhibiting calcium phosphate precipitation and dissolution, these compounds (*namely: *diphosphonates, Preliminary Relief Judge)*
> *were able not only to prevent ectopic calcification, but in contrast to pyro-phosphate (i.e. substances with P-C-P P-O-P instead, Preliminary Relief Judge) they also inhibited actual bone resorption. Further unlike pyrophosphate, diphosphonates were active when given both parenterally and orally. The way to their clinical use was set.*

On this matter, inter alia, the article further describes the following under the heading *Effect on bone resorption*:

> *In contrast to pyrophosphate, diphosphonates are extremely active in inhibiting bone resorption. (...) Of all the compounds tested, the $Cl_2$MDP (namely, clodronate, Preliminary Relief Judge) is the most potent.*
> *Strong effects are also seen* in vivo*.*
> *(...)*
> *"A great number of diphosphonates have been investigated for their inhibitory effect on bone resorption. It appears that increasing the chain length of the C-backbone*




> *increases activity until a length of about 9 carbon atoms is reached (Shinoda et al., 1979) Adding a hydroxyl group at position 1 also increases the effect (Shinoda et al., 1979) The amino-derivatives such as the 3-amino-1-hydroxypropane-1, 1-diphosphate (AHDP)*




*(that is the C-3 compound, pamidronate, Preliminary Relief Judge) are also very active (Lemkes et al., 1978; Shinoda et al., 1979; Reitsma et al., 1980) The relative activity of some of the diphosphonates tested is as follows: AHPDP > long chain 1-hydroxy diphosphonates > $Cl_2$MDP > EHDP (Shinoda et al., 1979).*

Fleisch closes his contribution with the conclusion that:

*The diphosphonates are very potent inhibitors of mineralisation and bone resorption. These characteristics have opened the way to the use of these compounds in disorders of ectopic calcification and of increased bone destruction. It would not be surprising if the first compounds tested are by no means optimal and that a further exploration of other types of diphosphonates could lead to a fruitful future development of a new class of drugs."*

From this publication of Fleisch it follows that at the time of the priority date (April 1982) it was part of the average skilled man's baggage that a) bisphosphonates in general are very active in the area currently under discussion, b) an extension of the carbon chain to C-9 seems to involve an increase in the activity concerned, c) adding a hydroxy group to the 1 position (instead of an H on that position) increases the effect, and that d) adding an amino group at the end of the carbon chain, as in the case of pamidronate, also promotes activity. The skilled man also finds a clear incentive to research other types of bisphosphonates for their usefulness in this field – for example, as a provisional opinion, it teaches the skilled man bisphosphonates having a carbon chain of 4 to 9 C atoms with one OH group on the 1 position and a $NH_2$ group at the end of the chain, at least bisphosphonates from the group of known bisphosphonates.

3.4 On the priority date the skilled man knew other bisphosphonates with the described characterising groups as substances, including the C-4 compound, alendronate, described inter alia in the publication of Kabachnik et al., *Synthesis and acid-base and complexing properties of amino-substituted α-hydroxyalkylidenediphosphonic acids* from February 1978 and EP 0 039 033 (hereafter: EP '033 or Blum), with 4 November 1981 as the date of publication. In Blum an improved route is given for synthesizing C-4 to C-6 compounds with a hydroxy group on the 1 position and an amino group at the end of the carbon chain. Incidentally, it evidently did not become clear in the proceedings before the Board of Appeal that in Kabachnik – in which alendronate is described as a substance – there is a clear reference for the use of (inter alia) this substance *(find various uses)* to an article by Vel'tishchev et al. (with Kabachnik as co-author) of April 1974 , in translation *Some perspectives on the clinical study and therapeutic use of phosphonic compounds*. In the latter article it is then unequivocally indicated that bisphosphonates are used in the treatment of bone diseases, and why. The Board of Appeal focuses on Blum and holds that it did not contain such a use. Apart from the question whether the reasoning of the Board, which will be tested more closely in the proceedings on the merit, is valid, this is not automatically conclusive for the question of inventive step, as a provisional opinion, in the light of the combined disclosure of Kabachnik and Vel'tishchev, because there already are clear guidelines for the skilled man in the Russian publications on the use of inter alia alendronate,

disclosed byKabachnik, as the active substance in a medicine for the treatment of bone diseases, reported at length in Vel'tishchev, which has not been taken into account by the Board in a knowable way in the grounds for the decision.

3.5 On the priority date, the skilled man was also familiar with US 4,304,734 (Jary) from December 1981, which describes (a synthesizing route for) neridronate, a new bisphosphonate with a longer carbon chain, the aforementioned C-6 compound with an OH-group at the 1-position and an $NH_2$-group at the 6-position. From that, the skilled man learns about the neridronic acid and its salts (neridronates)

> *are capable of regulating metal cations content (especially calcium content) in human organism thus enabling to cure diseases connected with content and circulation of these cations in organisms. Thus they (...) retard bone decalcification etc.*

Thus, US '734 indicates that neridronate can be used in pharmaceutical preparations for treating bone decalcification (*enabling to cure in human organism* and *retarding bone decalcification*).

3.6 The skilled man also knew on the priority date that, in a study by Felix, presented in November 1981 during a symposium in Nyon (this is not mentioned in the introduction to the description of the patent or involved in the evaluation by the Board of Appeal), promising *in vivo* results were achieved with this neridronate, also referred to in Felix' presentation with AHHexDP. From the results of this study, the skilled man learns, among other things:

> *In its efficacy on bone resorption AHHexDP is thus similar to dichloromethanediphosphonate (*in other words *clodronate* or *$Cl_2$MDP , Preliminary Relief Judge), more effective than ethane-1-hydroxy-1,1-diphosphonate (*sc. *etidronate* or *EHDP, Vzr.), but less effective than 1-hydroxypentane-1,1-diphosphonate and 3-amino-1-hydroxypropane-1,1-diphosphonate (*or *pamindronate* or *AHPDP, Preliminary Relief Judge).*

Felix' *Summary* reads as follows:

> *AHHexDP, a new diphosphonate, is characterized by a relatively low cellular toxicity in vitro, and a conspicuous inhibitory effect on bone turnover in vivo. It might thus have therapeutic applications in diseases with increased bone turnover.*

That involves, on the one hand, a *relatively low cellular toxicity in vitro* - contrary to what the skilled man would expect on the basis of the *Discussion* from the overview article by Fleisch published earlier that year, in which Fleisch himself refers to extreme (mortal) toxicity *in vitro* of longer chains, but also of pamidronate - while Felix also indicates that neridronate gives the same results in this *in vivo* study as clodronate, better than with etidronate, but less than with pamidronate. As a provisional opinion, the skilled man will find this to be an inducement to conduct further research into bisphosphonates with a longer C chain than pamidronate.

3.7 If the skilled man combines these publications (Fleisch and Felix) from the closest prior art for pharmaceutical preparations for the treatment of bone diseases, then, as a provisional opinion, there can be no inventive step relevant to patent law. If, with Merck, pamidronate is assumed to be the most effective bisphosphonate, which however, had rather serious side effects, and thus as the closest prior art (at least, the party experts engaged by Teva also seem to assume that, although during arguments,

Teva argued that Katatsjnik and/or Fleisch and/or Felix and/or Blum were the closest prior art), then the skilled man will find a clear inducement in Fleisch's article to a) examine other bisphosphonates as to their applicability in preparations for bone diseases, preferably with b) a longer carbon chain up to C-9 because the expectation expressed by Fleisch of greater effectivity, which according to Felix, with regard to neridronate (C-6) when compared to pamidronate (C-3), may not have led to increased effectivity, but from which it does follow that results usable *in vivo* can be obtained with a longer carbon chain, a longer chain which, in addition, contrary to the discussion from Fleisch's article from 1981 according to Felix' study, which was presented at the end of that year, gives acceptable toxicity *in vivi* (whereby the skilled man will realise that it follows form Fleisch's article that the *in vitro* toxicity in that article of both pamidronate and longer chains such as neridronate, was considered to be problematic). Since Blum teaches the skilled man an improved synthesizing route for C-4 to C-6 compounds with an OH at 1 and an $NH_2$ at the final position of the carbon chain, the skilled man will, without any inventive labour, arrive at the testing of in any event, these known C-4 and C-5 compounds, in view of the results achieved by Felix and the indication from Fleisch and Shinoda that longer chains may have better results. Certainly, this is – as a provisional opinion – true in view of the problematic side effects of the bisphosphonate preparation that until then worked the most effectively against bone diseases, pamidronate. That this is a step that is obvious to the average skilled man, in the provisional opinion, is even more clear in light of the aforementioned Russian publications, which, through a direct reference connect *the application* of, among other things, alendronate, with an older article about bisphosphonates which discusses research concerning *the use of these compounds in medicines against bone diseases*. In the provisional opinion, in the proceedings before the Board of Appeal, this seems to have been insufficiently considered. Merck's assertion that the skilled man will not make this connection between the Russian publications, is rejected, if only because of the direct reference in Kabachnik to Vel'tishchev, of which latter publication moreover, Kabatjsnik is co-author.

3.8 From a different perspective: Despite the fact the Felix demonstrates less effectiveness of the C-6 compound than the starting point, the C-3 compound, in the provisional opinion, Fleisch's encouragement to use a longer chain than C-3 to increase effectiveness nonetheless remains intact. After all, the skilled man is encouraged with regard to C-4 through C-9, and according to the Felix publication, was only falsified for C-6. A contra-indication for the use of longer chains from Fleisch, namely possible increasing toxicity was however, falsified by Felix, at least for C-6 and thus in any event partially. In the provisional opinion, this forms an additional indication for the skilled man to, in any event, try a longer chain than C-3 in the area between C-3 and C-6, such as C-4 and C-5, substances that were already known from, among other things, the synthesis according to Blum. Fleisch, in combination with Felix does not, as Merck alleges, specifically constitute a *teaching away* in view of the decreased effectiveness. In the provisional opinion, the mere result of Felix is insufficient for that purpose. As a provisional opinion, the skilled man on the other hand, is encouraged to turn to the application of C-4 and C-5 bisphosphonates for preparations for the treatment of bone diseases in such a way, that there is a *would* instead of *could* in the sense of the inventive step case law of the EPO: In the light of Fleisch and Felix, the skilled man would have tried alendronate, starting from pamidronate, in the hopes of resolving the problem of finding a more effective compound against bones diseases than pamidronate and in light of those publications, he has a *reasonable expectation of success*.

3.9 In particular, the skilled man would not have derived from the reduced effectiveness of neridronate compared to pamidronate, discovered by Felix, based on assumptions and without routinely conducting research into that, that there was a linear (decreasing) relation in the bisphosphonates with the aforementioned characteristic OH- and $NH_2$

groups in the C-3 to C-6 range. Invoking its submitted party expert reports, Teva has asserted that the skilled man would not assume this linear relation, which assertion has not or insufficiently been refuted, an assertion that it also made successfully before the English court, and that it also substantiated during the oral hearings in these preliminary relief proceedings on the basis of notes by Russell made during *cross examination* before the English court, in which he indicated that a linear decreasing connection is only one of the four possibilities, which the skilled man can verify only through experiments, but cannot predict. The written statement made by the other party expert presented by Teva, Roger Newton, also confirms that. Among other things, Merck submits against this that although it is true that the Board of Appeal did not take into account in so many words the publications by Fleisch and Felix which are in the center of attention in the foregoing, but that it must be examined for example, what Fleisch refers to, insofar as relevant in particular Shinoda et al. from 1979 and according to Merck, Shinoda was taken into account. It is correct that in the article published before the priority date *Structure-activity relationship of diphosphonates with alkyl groups of various lengths*, Shinoda indicates, among other things, the following (with Felix and Fleisch as co-authors, by the way):

> *Inhibition of crystal formation decreased with increasing chain length. Inhibition of crystal dissolution, however, was increased with increasing chain length with the exception of (...) EHDP which displayed the strongest inhibitory activity. The presence of an OH group at the C-1 position increased the inhibition of both crystal formation and dissolution. In calvaria cell cultures, lactate production was inhibited with smaller chain length but enhanced with larger alkyl groups. An OH group at the C-1 position increased the potency of this effect. The number of the above bone cells decreased with all diphosphonates, the effect being greater with increasing chain length. The addition of an OH group again increased this effect. In whole calvaria cultures, long-chain DP's inhibited bone resorption, but increased lactate production, while EHDP and (...) $Cl_2$MDP inhibited both, suggesting that the effect on bone resorption may not be correlated with the effect on lactate. In the growing rat, diphosphonates with the alkyl groups $C_4H_9$ to $C_8H_{17}$ inhibited bone resorption very strongly, especially when an OH group was on the C-1 position. Longer chain lengths were less active. Toxicity increased with chain length. The inhibition of mineralization decreased with chain length but increased when an OH group was present. Thus, a good correlation exists between inhibition of mineralization* in vitro *and* in vivo; *however, no correlation was found between bone resorption* in vivo *and findings* in vitro.

With Shinoda, however, that was not the end of it on the priority date, Fleisch (as stated, co-author of Shinoda), in his later overview article, added the indicated evaluations to that, even though he also refers to Shinoda, that does not mean that the skilled man would only take Shinoda to heart and ignore Fleisch's additions for the rest. The fact that various parameters pointed in contradictory directions, should have been clear to the skilled man from Shinoda. In Fleisch, however, there were additional clues for the skilled man for the search for better medication against bone diseases, in which one of the questions is that an acceptable balance must be found between factors that prevent resorption and avoid the inhibition of mineralization as much as possible. The fact that this itself is an inventive task is not at discussion, the issue is whether the skilled man proceeding from pamidronate with Fleisch and Felix in hand and in view of the rest of the relevant prior art indicated above, will arrive at the application of alendronate without inventive labour. In the provisional opinion, that is the case. The objection by Merck during the oral hearings that Fleisch does indicate that a) chain extension, b) the introduction of a hydroxy group at 1 and c) the addition of an amino group are beneficial, but that that does not state what or which way the skilled man should choose,

is rejected. It is obvious to do all three and when proceeding from pamidronate, the chain need only be extended by a single carbon atom.

3.10 In the provisional opinion, this is insufficiently affected by that which Merck submits against that considered above. If the Board had demonstrably taken into account the doctrine from, in particular, Shinoda (that it allegedly did so with a different publication by Fleisch from after the priority date, if true, is in any event irrelevant because of this tardiness), then it did not do so properly, also in view of the prior art that has been disclosed since then. For now, the opinion is that the Board insufficiently determined or was able to determine the value of this prior art during the assessment of inventive step. Insofar as Merck, finally, invokes the publications that were tardy in view of the priority date, these are irrelevant to the assessment for that reason alone.

3.11 Since, on the basis of the foregoing, there is already considered to be a realistic chance that the outcome of the proceedings on the merits will be that NL ‘562 is/was null and void, so that Merck has no rights under the SPC, Merck’s claims fail because of that and the other defences need not be discussed. As the party against whom a decision is given, Merck will be ordered to pay the costs of these proceedings.

**DECISIONS:**

The Preliminary Relief Judge:

- rejects the claims;

- orders Merck to pay the costs of these proceedings, estimated up to this decision on the part of Teva at EUR 244 in disbursements, and EUR 703 in local counsel fees.

This decision was rendered by *mr.* G.R.B. van Peursem and was pronounced at the public court session on 25 April 2005 in the presence of the clerk of the court.