Tramadol and convulsion, serotonin syndrome, suicide, dosing in the elderly and dosing in patients with renal or hepatic impairment
Final SmPC and PL wording agreed by PhVWP in July 2012

Doc.Ref.: CMDh/PhVWP/056/2012
July 2012

Annex 1

SUMMARY OF PRODUCT CHARACTERISTICS

Section 4.2

The dose should be adjusted to the intensity of the pain and the sensitivity of the individual patient. The lowest effective dose for analgesia should generally be selected.[...]

Geriatric patients
A dose adjustment is not usually necessary in patients up to 75 years without clinically manifest hepatic or renal insufficiency. In elderly patients over 75 years elimination may be prolonged. Therefore, if necessary the dosage interval is to be extended according to the patient's requirements.

Renal insufficiency/dialysis and hepatic impairment
In patients with renal and/or hepatic insufficiency the elimination of tramadol is delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements.

Section 4.5

Tramadol can induce convulsions and increase the potential for selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, antipsychotics and other seizure threshold-lowering medicinal products (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.

Concomitant therapeutic use of tramadol and serotonergic drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors (see section 4.3), tricyclic antidepressants and mirtazapine may cause serotonin toxicity. Serotonin syndrome is likely when one of the following is observed:

- Spontaneous clonus
- Inducible or ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia and body temperature > 38 °C and inducible or ocular clonus.

Withdrawal of the serotonergic drugs usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.

PACKAGE LEAFLET

Section 3 - How to take <tradename>

The dosage should be adjusted to the intensity of your pain and your individual pain sensitivity. In general the lowest pain-relieving dose should be taken. [...]

Elderly patients
In elderly patients (above 75 years) the excretion of tramadol may be delayed. If this applies to you, your doctor may recommend prolonging the dosage interval.

Severe liver or kidney disease (insufficiency)/dialysis patients
Patients with severe liver and/or kidney insufficiency should not take <tradename>. If in your case the insufficiency is mild or moderate, your doctor may recommend prolonging the dosage interval.

Section 2 – What you need to know before you <take> <use> <tradename>

Taking other medicines

The risk of side effects increases,
- if you are taking medicines which may cause convulsions (fits), such as certain antidepressants or antipsychotics. The risk having a fit may increase if you take <tradename> at the same time. Your doctor will tell you whether <tradename> is suitable for you.
- if you are taking certain antidepressants. <tradename> may interact with these medicines and you may experience symptoms such as involuntary, rhythmic contractions of muscles, including the muscles that control movement of the eye, agitation, excessive sweating, tremor, exaggeration of reflexes, increased muscle tension, body temperature above 38 °C.

Dutch translation

SAMENVATTING VAN DE PRODUCTKENMERKEN

Rubriek 4.2

De dosering dient te worden aangepast aan de ernst van de pijn en de individuele gevoeligheid van de patiënt. In principe moet altijd de laagste analgetisch werkzame dosis worden gekozen [...]

Geriatrische patiënten
In de regel is een aanpassing van de dosering bij oudere patiënten (tot 75 jaar) zonder klinisch manifeste lever- of nierinsufficiëntie niet noodzakelijk. Bij oudere patiënten (ouder dan 75 jaar) kan de uitscheiding zijn verlengd. In dat geval dient het doseringsinterval aan de hand van de behoefte van de patiënt te worden verlengd.

Nierinsufficiëntie/ dialyse en leverfunctiestoornis
De uitscheiding van tramadol is vertraagd bij patiënten met nier en/of leverfunctiestoornis. Bij deze patiënten dient verlenging van het doseringsinterval zorgvuldig te worden overwogen, aan de hand van de behoefte van de patiënt.

Rubriek 4.5

Tramadol kan convulsies induceren en kan de kans vergroten op het veroorzaken van convulsies door selectieve serotonine-heropname remmers (SSRIs), serotonine-norepinefrine-heropname remmers (SNRIs), tricyclische antidepressiva, anti-psychotica en andere middelen die de aanvalsdrempel voor convulsies verlagen (zoals bupropion, mirtazapine, tetrahydrocannabinol).

Gelijktijdig therapeutisch gebruik van tramadol en serotonerge middelen, zoals selectieve serotonine heropname remmers (SSRIs), serotonine-norepinefrine heropname remmers (SNRIs), MAO-remmers (zie rubriek 4.3), tricyclische antidepressiva en mirtazapine kunnen serotonine toxiciteit veroorzaken.

De volgende verschijnselen kunnen duiden op een serotonine syndroom:

- Spontane clonus
- Induceerbare of oculaire clonus met agitatie of diaforese
- Tremor en hyperreflexie
- Hypertonie en lichaamstemperatuur > 38 ^{o}C en induceerbare of oculaire clonus.

Het staken van de behandeling met serotonerge geneesmiddelen zorgt meestal voor een snelle verbetering. Behandeling hangt af van de aard en ernst van de symptomen.

BIJSLUITERTEKST

Rubriek 3: Hoe wordt <productnaam> gebruikt?

De dosis wordt aangepast aan de ernst van uw pijn en aan uw persoonlijke gevoeligheid voor pijn. Over het algemeen moet de laagste dosis die de pijn verlicht worden gebruikt. […]

Oudere patiënten
Bij oudere patiënten (ouder dan 75 jaar) kan de uitscheiding van tramadol vertraagd zijn.
Als dit voor u van toepassing is, kan uw arts adviseren om het tijdsinterval tussen de doseringen te vergroten.

Patiënten met ernstige lever en/of nierziekte (insufficiëntie) /dialyse patiënten
Patiënten met ernstige lever en/of nierziekte dienen <productnaam> niet te gebruiken. Als er sprake is van een milde of matige insufficiëntie dan kan uw arts adviseren om het tijdsinterval tussen de doseringen te vergroten.

Rubriek 2: Wanneer mag u dit middel niet <gebruiken><innemen> of moet u er extra voorzichtig mee zijn?

<Gebruik u nog andere geneesmiddelen?<Neemt u nog andere geneesmiddelen in?>

De kans op bijwerkingen neemt toe

- als u geneesmiddelen inneemt die stuipen (aanvallen) kunnen veroorzaken, zoals bepaalde geneesmiddelen ter behandeling van een depressie of een psychose. De kans dat u een aanval krijgt kan toenemen als u tegelijkertijd < productnaam> gebruikt. Uw arts vertelt u of < productnaam > voor u geschikt is.

- als u bepaalde antidepressiva neemt. < productnaam > en deze geneesmiddelen kunnen op elkaar inwerken en u kunt symptomen ervaren zoals ongecoördineerde, ritmische samentrekkingen van de spieren, met inbegrip van spieren die bewegingen van het oog sturen, rusteloosheid, overmatig zweten, trillen, verhoogde reflex, verhoogde spanning van de spieren en lichaamstemperatuur boven 38^{o}C.

Annex 2

Summary Assessment Report of the PhVWP July 2012

Tramadol – Risk of adverse reactions of the central-nervous system and dosing in the elderly and those with renal or liver impairment

Key message

Updating the product information for tramadol has been recommended to minimise certain adverse reactions of the central-nervous system and to advise on dosing in the elderly and those with renal or liver impairment.

Safety concern and reason for current safety review

Following a safety review relating to tramadol conducted by the Italian competent authorities, the PhVWP agreed to review tramadol in relation to safety concerns, including dosing in elderly patients and in patients with renal or hepatic insufficiency as well as risks of seizures, serotonin syndrome and suicidal ideation and behaviour.

Clinical setting

Tramadol is a prescription-only medicine indicated for the treatment of moderate to severe pain. It is a centrally acting opioid analgesic, and other mechanisms contributing to its analgesic effect are inhibition of neuronal re-uptake of noradrenaline and enhancement of serotonin release.

Information on the data assessed

The data assessed included clinical and pharmacokinetic trial data, periodic safety update reports (PSURs) as well as spontaneous adverse reaction reports provided by the originator marketing authorisation holder. Two lists of questions were sent to the originator marketing authorisation holder, and their responses (including a review of the medical literature) were assessed as well.

Outcome of the assessment

The PhVWP considered the following:

<u>Dosing for patients older than 75 years of age</u>

The data from clinical trials that included elderly patients did not indicate that the frequency of adverse events observed in this age group was substantially higher than that for other age groups. Further, these data suggested that the daily dose needed for optimal pain relief with minimal adverse reactions is similar for the different age groups.

No relevant effect of age on the pharmacokinetics of tramadol in patients younger than 75 years of age was shown. However, in patients older than 75 years the elimination half-life of tramadol was prolonged by approximately 15% and the area under the curve (AUC; i.e. the overall amount of a medicine in the blood plasma) was increased by approximately 50% with high inter-subject variability. The mean maximum plasma concentration was 30% higher in patients older than 75 years which might represent an overdose in some patients.

the basis of these data, the PhVWP concluded that a recommendation for general dose reduction in patients older than 75 years was not justified. In particular it was considered that there was no scientific basis for reducing the maximum daily dose to 300 mg as recommended in the US prescribing information of tramadol.

The PhVWP took the view that the fact that elimination half-life might be prolonged in patients above 75 years of age is addressed in the current originator summary of product characteristics (SmPC) for tramadol-containing medicinal products authorised in the EU through the following advice: "If necessary the dosage interval is to be extended according to the patient's requirements". The available data did not allow more precise recommendations regarding extension of the dosing interval.

Overall, the PhVWP considered that lowering the maximum daily dose or specific dosing intervals could lead to under-dosing in some patients above 75 years of age.

Dosing for patients with renal or hepatic impairment

No specific risks were observed in clinical trials nor described in PSURs for patients with renal or hepatic impairment.

In patients with renal impairment, mean maximum plasma concentrations were approximately 20% higher, the AUC was considerably increased and terminal half-lives were prolonged. However, inter-subject variability was high and no relationship between the degree of renal impairment and AUC or terminal half-life was noted.

In patients with hepatic impairment of any degree, maximum plasma concentrations were up to 50% higher, which might represent an overdose in some patients. Smaller increases were observed in patients with mild to moderate impairment only. Mean AUC and terminal half-life were also considerably increased by up to 200%. There seems to be a relationship between the degree of hepatic impairment (Child Pugh A or B) on one side and mean AUC and terminal half-life on the other. However, inter-subject variability of pharmacokinetic parameters was high in patients with hepatic impairment. No clear relationship between all degrees of hepatic impairment and increase in mean AUC and terminal half-life were observed.

Given these data, the PhVWP concluded that a general dose reduction, lower maximum daily dose or increased dosing interval in patients with renal or hepatic impairment was not justified. In particular there seemed to be no scientific basis for specific recommendations in patients with a glomerular filtration rate (GFR) less than 30 ml/min or patients with cirrhosis or severe hepatic impairment.

The fact that elimination half-life might be prolonged in patients with renal or hepatic impairment was considered addressed in the current originator SmPC, which includes the advice that "In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements". Available data did not allow more precise recommendations regarding extension of the dosing interval.

Overall, the PhVWP considered that lowering the maximum daily dose or specific dosing intervals could lead to under-dosing in some patients with renal or hepatic impairment.

General dosing recommendations

The PhhWP noted that the current originator SmPC already contains an introductory statement in section 4.2 of the SmPC that "The dose should be adjusted to the intensity of the pain and the sensitivity of the individual patient." and further a statement in a 4.2 sub-section on adults and adolescents above the age of 12 years that "The lowest analgesically effective dose should generally be selected". The PhVWP concluded that the latter advice should be included after the sentence in the introductory statement.

Role of pharmaceutical formulations for dosing in general and for those with renal or hepatic impairment

Tramadol-containing medicinal products are available as immediate or extended release formulations. As the above conclusions regarding dosing are of general nature, they apply to both immediate and extended release formulations.

In the case of extended release formulations, a prolongation of the dosing interval might mean that tramadol is administered only once daily instead of twice daily.

With regard to patients with renal or hepatic impairment, the PhVWP noted that the current originator SmPC of the extended release formulation contains the statement "In cases of severe renal and/or hepatic insufficiency, tramadol prolonged-release tablets are not recommended".

Risk of convulsion

In addition to the patient groups described as being at higher risk of convulsion in the current originator SmPC, the PhVWP identified patients on certain concomitant medication as being at risk due to interactions. The following active substances, which are currently not explicitly mentioned in the SmPC section 4.5, were associated with interactions leading to convulsion in more than two spontaneous adverse reaction case reports: bupropion, mirtazapine, tetrahydrocannabinol and venlafaxine.

The PhVWP concluded that bupropion, mirtazapine and tetrahydrocannabinol should be added to section 4.5 of the SmPC, as well as the class of serotonin norepinephrine reuptake inhibitors (SNRIs), which includes venlafaxine and duloxetine, which has also been reported as an interacting substance leading to convulsion.

An analysis of substances with known potential to lower the seizure threshold for which two or less case reports of convulsion were received did not identify further classes of medicines or single substances warranting inclusion in SmPC section 4.5 at this time. However, the PhVWP concluded that all cases of interaction involving convulsion should be closely monitored on an ongoing basis and further classes or substances should be added to SmPC section 4.5 as necessary in the future.

Risk of serotonin syndrome

The literature review suggested that, apart from the concomitant administration of serotonergic medicines, there were no patient groups that have an increased risk of serotonin syndrome.

The following concomitant active substances or classes of substances with serotonergic potential were identified in more than two case reports of serotonin syndrome with tramadol: selective serotonin reuptake inhibitors (SSRIs), SNRIs, mirtazapine, tricyclic antidepressants (TCAs) and monoaminooxidase (MAO)-inhibitors.

The PhVWP noted that SSRIs and MAO-inhibitors are already included as serotonergic medicines in SmPC section 4.5, and concluded that SNRIs, mirtazapine and TCAs should be added to SmPC section 4.5, given the substantial number of case reports on interactions with the concerned active substances.

Analysis of serotonergic substances for which two or less case reports of serotonin syndrome were received did not identify further groups of drugs or single substances warranting inclusion in SmPC section 4.5 at this time.

Further, the PhVWP concluded that all interactions linked to serotonin syndrome should continue to be closely monitored and further substances or classes should be added to SmPC section 4.5 as necessary in the future.

The PhVWP endorsed the originator marketing authorisation holder's suggestion to replace the symptoms of serotonin syndrome in SmPC section 4.5 with the Hunter Serotonin Toxicity Criteria [1]. However a simpler presentation of the Hunter criteria was proposed.

Risk of suicidal ideation and behaviour

The PhVWP agreed that the present data did not support a causal relationship between tramadol and suicidal ideation or behaviour.

The PhVWP considered that this signal arose most likely due to the higher risk of suicidal behaviour of patients with (chronic) pain. In addition, in a large proportion of case reports of suicidal ideation or behaviour, patients were also using antidepressants (indicative of a history of depression) and/or had a history of psychiatric disorders. Psychiatric disorders, in particular depression, are associated with an increased risk of suicidal behaviour.

Moreover, a part of the case reports might be due to the possibility that tramadol is used alone or in combination with other substances as a means to commit suicide. This is supported by the large proportion of cases where tramadol was reported to have been used only once and by the finding that there is disproportional reporting for medical events closely related to suicidal acts but not to suicidal or self-injurious ideation or suicidal depression.

Likewise, the low affinity of tramadol for binding to or inhibiting the serotonin transporter does not support the concept that tramadol exerts similar effect as observed for SSRIs and therefore cannot be considered to have a similar risk of suicide.

The PhVWP therefore concluded that a warning regarding the use of tramadol in patients who are suicidal, suffering from emotional disturbances or depression, as introduced in the US prescribing information in 2010, was disproportionate at this time, also considering that other medicines with potential for suicide do not carry a similar warning and that there was no evidence that tramadol is used more frequently in suicidal acts.

Recommendations for the product information

Given the conclusions above, the PhVWP recommended that the product information of all tramadol-containing products authorised in the EU should be updated to include,

in SmPC section 4.2, that:

- the dose should be adjusted to the intensity of the pain and the sensitivity of the individual patient and the lowest effective dose for analgesia should generally be selected;

- a dose adjustment is not usually necessary in patients up to 75 years of age without clinically manifest hepatic or renal insufficiency; in elderly patients over 75 years elimination may be prolonged; therefore, if necessary, the dosing interval is to be extended according to the patient's requirements;

- in patients with renal and/or hepatic insufficiency the elimination is delayed and prolongation of the dosing interval should be carefully considered according to the patient's requirements.

in SmPC section 4.5, that:

- tramadol can induce convulsions and increase the potential for SSRIs, SNRIs, TCAs, antipsychotics and other seizure threshold-lowering medicinal products (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions;

- concomitant therapeutic use of tramadol and serotonergic medicines, such as SSRIs, SNRIs, MAO inhibitors (see SmPC section 4.3), TCAs and mirtazapine may cause serotonin toxicity; serotonin syndrome is likely when one of the following is observed: spontaneous clonus, inducible or ocular clonus with agitation or diaphoresis, tremor and hyperreflexia, hypertonia and body temperature >38°C and inducible or ocular clonus; withdrawal of the serotonergic medicines usually brings about a rapid improvement; treatment depends on the type and severity of the symptoms;

in the package leaflets (PLs), that:

- the dosing should be adjusted to the intensity of the pain and individual pain sensitivity; in general the lowest pain-relieving dose should be taken;

- in elderly patients (above 75 years of age) the excretion of tramadol may be delayed; and if this applies, the physician may recommend prolonging the dosing interval;

- patients with severe liver and/or kidney insufficiency should not take tramadol; if the insufficiency is mild or moderate, the physician may recommend prolonging the dosing interval;

- the risk of adverse reactions increases, if one is taking medicines which may cause convulsions, such as certain antidepressants or antipsychotics; the risk of convulsion may increase if one takes tramadol and one of these medicines at the same time; the physician will tell the patient whether tramadol is suitable, if one is taking certain antidepressants; tramadol interacts with these medicines and one may experience symptoms such as involuntary, rhythmic contractions of muscles, including the muscles that control movement of the eye, agitation, excessive sweating, tremor, exaggeration of reflexes, increased muscle tension, body temperature above 38°C.

References

[1] Dunkley EJ, Isbister GK, Sibbritt D, Dawson AH, Whyte IM. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. QJM. 2003; 96: 635-642.

Registratiehouder
(t.a.v. registratieafdeling)

Your letter	Your reference	Utrecht,
--	--	..
Case number	Our reference	
	../../	
Case manager	Telephone number	

Subject
Request for change in the product information following the PhVWP/CMDh decision

Tramadol – Risk of adverse reactions of the central-nervous system and dosing in the elderly and those with renal or liver impairment.

Following assessment of the available data assessed by the PhVWP on Tramadol and convulsion, serotonin syndrome, suicide, dosing in the elderly and dosing in patients with renal or hepatic impairment, all Marketing Authorisation (MA) holders for products with tramadol as active ingredient are being requested to submit type IB variations (variation number C1.3.a) (or equivalent national procedures – see below) for their relevant products to implement the PhVWP/CMD(h) decision

Link to the website with the published decision: http://www.hma.eu/222.html

You are requested to change the SmPC and Package Leaflet (PL) of

<product> < RVG>

The agreed texts, together with the translation in Dutch, are attached to this letter.

These texts should be included literally in the SmPC and PL. However, you are requested to check the SmPC and PL carefully to make sure that there is no overlap with the current texts. If there is such overlap, you should replace the current text with wording from the agreed texts.
With regard to PL wording, further user testing by individual MA holders will not be expected on this occasion.

For products registered via an MRP or DCP procedure, the RMS takes responsibility on behalf of the CMSs to request the variation from the MA holder and initiate the procedure.

The applications do not require supporting information or expert statements and will be accepted by Member States Competent Authorities without further assessment or amendment.

If there is no reason to update your product information via a type IB variation, you are requested to reply to this letter with a statement that the product information does not need to be changed.

How to submit this variation in the Netherlands

The MEB has pre-assigned you the following case number for this variation: <XXXXX>. You are requested to send your application data package and future correspondence to the case@cbg-meb.nl e-mail address.

Please mention the following information.

'Subject' field of the e-mail:
- Case <XXXXX>
- Name of the medicinal product and RVG number or Procedure number (if NL=RMS)

Message body:
- Case <XXXXX>
- Implementation of the PhVWP/CMD(h) decision on request of the MEB.

Attachments:
- Completed application form
- Checked guideline regarding the variation
- Product information (SmPC, PL and/or labeling, if applicable) affected with this variation (tracked and clean versions in Word format).

If the product was registered via MRP/DCP with NL = RMS, you are also asked to include a dispatch list with the submission dates in the CMSs. Please, be informed that you have to submit in such case, both the English texts and the national translations.

Timetable for implementation
You should submit variations no later than 1 October 2012.

On behalf of the Medicines Evaluation Board
in the Netherlands,

Drs. A.H.P. van Gompel

This notification has been produced centrally in an automated process and consequently does not bear a signature.

Attachments:
Annex 1: Agreed texts (UK and Dutch versions)
Annex 2: Summary assessment report