Public Assessment Report

Name of the Product:

DORETA
37.5 mg/325 mg and 75 mg/650 mg film-coated tablets

(tramadol hydrochloride/paracetamol)

Procedure number:
HU/H/0190/001-002

Marketing authorisation holder: Krka d.d. Slovenia

Date: 26 April 2013

CONTENT

LAY SUMMARY

The reference and concerned member states, after carefuls assessment of their quality and therapeutic benefit/risk ratio have issued marketing authorisation for Doreta 37.5 mg/325mg and 75 mg/650mg film-coated tablets. The holder of the marketing authorisation is Krka d.d. (Slovenia).

What Doreta is and what it is used for

Doreta is a combination of two analgesics. The active substances are tramadol (in hydrochloride salt); it is a narcotic-like pain killer. Paracetamol is a less potent pain reliever that increases the effects of tramadol.

The other ingredients are pregelatinised maize starch, sodium starch glycolate (type A), microcrystalline cellulose and magnesium stearate in the tablet core, and hypromellose, titanium dioxide (E171), macrogol 400, yellow iron oxide (E172), iron oxide red (E172) only in strength 75mg/650mg and polysorbate 80 in the film-coating.

The tablets are intended for use in the treatment of moderate to severe pain when your doctor recommends that a combination of tramadol and paracetamol is needed.

The 37.5mg/325mg film-coated tablets are yellow-brown, oval, and slightly biconvex packed in blisters.

The 75mg/650mg film-coated tablets are slightly orange, oval, biconvex, film-coated tablets widely scored on both sides.

Before you take Doreta

Do not take Doreta if you
- are allergic (hypersensitive) to paracetamol, tramadol or any of the other ingredients,
- drink alcohol,
- take any medicine that can make you sleepy or less alert; these include opioid-containing pain relievers such as morphine and codeine,
- are currently taking monoamine oxidase inhibitors (MAOIs) for e.g. depression or have taken any MAOIs within the last two weeks,
- suffer from severe liver problems,
- have epilepsy that is not adequately controlled on your current medicine.

Take special care with if you
- have kidney problems,
- have liver problems or alcoholic liver disease or you have noticed your eyes and skin turning yellow, which may suggest jaundice or problems with bile ducts,
- have difficulty breathing, for example, asthma or lung problems,

- are dependent on any other medicines used to relieve moderate to severe pain, for example, morphine,
- are epileptic or have you experienced fits or seizures,
- have suffered from a head injury, shock or severe headaches which may or may not be associated with vomiting,
- take other medicines containing paracetamol or tramadol.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Doreta should not be taken together with the following:
- monoamine oxidase inhibitors (MAOIs),
- opioid-containing pain relievers such as morphine and codeine.

Doreta is not recommended to be taken with the following:
- carbamazepine, commonly used to treat epilepsy or facial neuralgia (severe pain attacks in the face),
- opioids, used to treat moderate to severe pain, e.g. buprenorphine, nalbuphine and pentazocine.

In certain circumstances, Doreta may be taken with the following medicines:
- serotonin reuptake inhibitors (SSRIs), used to treat depression. Serotonin Syndrome has been reported in a temporal connection with the therapeutic use of tramadol in combination with other serotoninergic medicines such as selective serotonin re-uptake inhibitors and triptans. Signs of Serotonin Syndrome may be for example, confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhea,
- certain morphine-like medicines used, for example, to prevent or relieve coughing,
- sedatives, for example, benzodiazepines,
- sleeping pills, for example, barbiturates,
- certain medicines used to lower blood pressure,
- thalidomide,
- baclofen, used as a muscle relaxant,
- warfarin, used to thin the blood,
- CYP3A4 inhibitors, for example, ketoconazole (an antifungal) or erythromycin (an antibacterial),
- bupropion, used to help people to stop smoking,
- tricyclic antidepressants,
- tranquillisers.

Taking the following medicines together with Doreta may affect how Doreta works in your body:
- metoclopramide and domperidone, used in nausea and vomiting,
- cholestyramine, used to treat diarrhoea and itchy skin.

Tell your doctor or dentist that you are taking Doreta before you have a general anaesthetic.

Doreta can be taken with *food and drink*. Doreta itself may make you feel drowsy but a concomitant alcohol intake may make you feel drowsier. Alcohol increases the sedative effect of opioid analgesics, the effect on alertness can make driving of vehicles and the use of machines dangerous, avoid intake of alcoholic drinks and of medicinal products containing alcohol.

Pregnancy and breast-feeding: since Doreta is a fixed combination of active ingredients including tramadol, it should not be used during pregnancy and breast feeding.

Driving and using machines: do not drive, operate machinery or perform other activities for which you need to be alert until you know how Doreta affects you. It may make you feel drowsy.

How to take Doreta

The usual starting dose is two tablets. If required, further doses can be taken after every six hours, as recommended by your doctor.

Do not take more than 8 tablets of 37,5 mg/325 mg tablets and 4 tablets of 75mg/650mg per day (equivalent to 300 mg tramadol and 2600 mg paracetamol).

If you have a history of kidney or liver problems, your doctor may increase the time between doses.

Doreta is not recommended for use in children under 12 years.

In patients over 75 years old, it is recommended that the minimum interval between doses should be not less than 6 hours, due to the presence of tramadol.

The tablets must be swallowed with some liquid. They should not be broken or chewed.
The tablets should be taken for as short a time as possible.

If you think that the effect of Doreta is too strong (i.e. you feel very drowsy or have difficulty with breathing) or too weak (i.e. you have inadequate pain relief), contact your doctor or pharmacist. If your symptoms do not get any better, see your doctor.

If you take more Doreta tablets than you should: immediate medical advice should be sought in the event of an overdose, even if you feel well, because of the risk of delayed, serious liver damage.

If you forget to take Doreta: do not take a double dose to make up for a forgotten tablet. If you miss a dose, take your next tablet at the usual time.

If you stop taking Doreta: if you have been using it for some time, you should talk to your doctor if you want to stop because your body may have got used to it. If you do suddenly stop using Doreta you may feel unwell. You may experience anxiety, agitation, nervousness, sleeplessness, hyperactivity, tremors and/or an upset stomach.

Possible side effects

Like all medicines, Doreta can cause side effects, although not everybody gets them.

In rare cases (occurring in less than one out of 1000, but in more than one out of 10,000 treated individuals), using a medicine of this type may make you become dependent on it, making it hard to stop taking it. You may experience withdrawal symptoms such as agitation, anxiety, nervousness, sleeplessness, hyperactivity, tremors and/or an upset stomach. If you do notice any of these effects, or any other unusual symptoms, please tell your doctor or pharmacist as soon as possible.

The very common (occurring in more then one out of 10 treated individuals) side effects may include:
- nausea,
- dizziness,
- drowsiness.

These are usually mild and not troublesome.

Common (occurring in less than one out of 10, but in more than one out of 100 treated individuals) side effects may include:
- vomiting,
- constipation,
- flatulence,
- diarrhoea,
- stomach pain,
- digestion problems,
- a dry mouth, headache,
- shaking,
- confusion,
- sleep disorders,
- mood changes (anxiety, nervousness, euphoria (a sense of feeling "high" all the time),
- increased sweating,
- itching.

Uncommon (occurring in less than one out of 100, but in more than one out of 1000 treated individuals) side effects include:
- high blood pressure, heart rhythm and heart rate disorders,
- difficulty or pain on passing urine/protein in the urine,
- skin reactions/hives,
- ringing in the ear,
- depression,
- nightmares,
- hallucinations (hearing, seeing or sensing things that are not really there),
- loss of memory,
- difficulty swallowing,
- blood in the stools,

- shivers,
- hot flushes,
- pains in the chest,
- uncoordinated movement,
- muscle cramps,
- unusual tingling feeling ("pins and needles"),
- convulsions,
- drug dependence,
- blurred vision,
- shortness of breath,
- raised liver enzymes.

How to store Doreta tablets

This medicinal product does not require any special storage conditions but keep them out of the reach and sight of children.

Scientific discussion

This module reflects the scientific discussion for the approval of Doreta 37.5 mg/325mg and 75 mg/ 650mg film-coated tablets.
The procedure was finalised at 05 April 2009 (the 37.5 mg/325mg strength), at 19 February 2011 (the 75 mg/650 mg strength) and at 9 August 2012 (repeat-use procedures for both strengths).
For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, implemented by the Act CXV of 2005 *on Medicinal Products for Human Use and on the Amendment of Other* R*egulations Related to Medicinal Products* as well as by the Decree 52/2005 (IX. 18.) of the Minister of Health *on placing medicinal products for human use on the market* in Hungary, an application has been submitted to the reference and competent authorities of the Member State concerned.

This Decentralised Procedure application, filed in 2009 (Reference member state, RMS: Hungary, concerned member states, CMS: Czech Republic, Latvia, Lithuania, Poland, Romania, Slovenia and Slovakia) concerned the generic version of Doreta 37.5 mg/325 mg, a paracetamol/tramadol hydrochloride fixed-dose combination film-coated tablets.

The application was submitted according to Article 10(1) of Directive 2001/83/EC (generic application) and therefore contained no new clinical or preclinical data, other than supporting literature where necessary. The originator product was Zaldiar 37.5 mg/325 mg (Grunenthal, Germany), authorised for marketing since 2002 in the European Union. They are now marketed under different names in several countries of the European Union (i.e. Czech Republic, Germany, Latvia, Poland, Portugal, Romania, Slovakia, Slovenia as well as since 2008 Hungary).

After granting the marketing authorisation, another Decentralised Procedure (RMS: Hungary, CMSs: Bulgaria, Czech Republic, Estonia, Latvia, Lithuania, Poland, Romania, Slovenia and Slovakia) application concerning Doreta 75 mg/650 mg film-coated tablet was submitted in 2011. The legal basis of this second application was Article 10(3) of the Community code (hybrid application), line extension.

Later, two repeat-use procedures completed the marketing authorisations in 2012 (RMS: Hungary, CMSs for the 37.5 mg/325 mg strength: Bulgaria, Estonia, France, Spain and United Kingdom, CMSs for the 75 mg/650 mg strength: Estonia and France).

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Doreta 37.5 mg/325 mg and 75 mg/650 mg film-coated tablets. The holder of the marketing authorisation is Krka d.d. (Slovenia).

The products are indicated for the symptomatic treatment of moderate to severe pain for patients whose pain is considered to require a combination of tramadol and paracetamol.

The maximum daily dose recommended in the SmPC is 300 mg tramadol, 2600 mg paracetamol.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

This application by Krka, d.d. for a marketing authorisation, via Decentralised Procedure with Hungary as Reference Member State (RMS), concerns an abridged application according to the article 10.1 of consolidated Directive 2001/83/EC (i.e. a generic application) for Doreta 37.5 mg/325 mg film-coated tablets than a hybrid application for Doreta 75 mg/650 mg film-coated tablets according to Article 10.3 of the Directive.

The products consist of the weak opioid tramadol and the non-opioid paracetamol, combining two known and well-established analgesic agents.

Tramadol and paracetamol combinations as film-coated tablets were first introduced in the human therapy in France in 2002, named Zaldiar 37.5 mg/325 mg film-coated tablets and by now are marketed under different names in several countries of the European Union (i.e. Czech Republic, Germany, Latvia, Poland, Portugal, Romania, Slovakia, Slovenia as well as since 2008 Hungary). A bioequivalence study has been performed using the innovator product Zaldiar 37.5 mg/325 mg (Grunenthal, Germany).

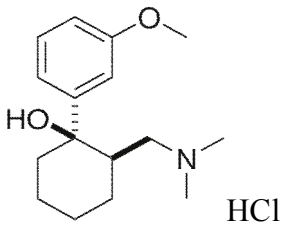
II.2 Drug Substances

II.2.1 Tramadol hydrochloride

The Applicant has submitted two European Pharmacopoeia (Ph. Eur.) Certificates of Suitability (CEP) for the drug substance tramadol hydrochloride. The CEPs indicate that the Ph. Eur. monograph is suitable to control the purity of the substance, provided that they are supplemented with a test for the residual solvents by GC.

International non-proprietary name (INN):	tramadoli hydrochloridum
Ph.Eur. name:	tramadol hydrochloride
Chemical name:	(1RS,2RS)-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride

Structural formula:



The active substance is white or almost white crystalline powder. It is freely soluble in water and in methanol, very slightly soluble in acetone.

The substance is specified according to the requirements of the current Ph. Eur. monograph; additional specification has only been set for residual solvents.

The Ph. Eur. specification includes the following tests for tramadol hydrochloride: identification (IR, melting point, TLC, chlorides), clarity and degree of opalescence of solutions, degree of coloration of solutions, acidity, optical rotation, related substances (HPLC), heavy metals, water content, sulphated ash and assay (HPLC). Residual solvents (GC) are also controlled. The specification is in accordance with the Ph. Eur. general monograph on *Substances for pharmaceutical use* and the ICH Q6A guideline.

The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. Residual solvent method not described in the Ph. Eur. is adequately drawn up and sufficiently validated.

Reference materials used for the control of the substance are adequately characterized and evaluated by EDQM.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

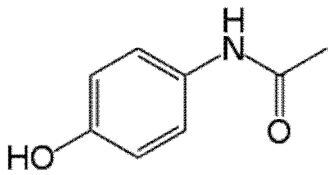
The proposed retest periods of 5 years are covered by CEPs, if stored in double PE bags and in a fibre drum.

GMP compliance of the API manufacturers is demonstrated by the applicant.

II.2.2 Paracetamol

The Applicant has submitted two CEPs for the drug substance paracetamol. The CEPs indicate that the Ph. Eur. monograph is suitable to control the purity of the substance.

International non-proprietary name (INN): paracetamolum
Ph.Eur. name: paracetamol
Chemical name: N-(4-Hydroxypheny)acetamide
Structural formula:



The active substance is white or almost white crystalline powder. It is sparingly soluble in water, freely soluble in alcohol, very slightly soluble in methylene chloride.

The substance is specified according to the requirements of the current Ph. Eur. monograph.

The Ph. Eur. specification includes the following tests for paracetamol: identification (IR, specific absorbance, melting point, colour reaction, reaction of acetyl), related substances (HPLC), heavy metals, loss on drying, sulphated ash and assay. The specification is in accordance with the Ph. Eur. general monograph on *Substances for pharmaceutical use* and the ICH Q6A guideline.

The specifications reflect all relevant quality attributes of the active substance and were found to be adequate to control the quality of the drug substance. Reference materials used for the control of the substance are adequately characterized and evaluated by EDQM.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

The proposed retest periods of 5 years are supported by the submitted stability data, if stored in PE bags and in a fibre drum.

GMP compliance of the API manufacturers is demonstrated by the applicant.

II.3 Medicinal Product

The aim of the development was to formulate a generic alternative to the authorised pharmaceutical product Zaldiar tablets (Grunenthal, UK). The qualitative composition (except colour red iron oxide) and the manufacturing process for both strengths are the same as well as the manufacturing equipment. The same granule is used for the higher strength as well.

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided. The compositions and the pharmaceutical tests evaluated during development of the final formulations are included in the documentation.

The excipients used in the finished products are pregelatinised starch, sodium starch glycolate (Type A), microcrystalline cellulose, magnesium stearate. The film-coating contains titanium dioxide, hypromellose, macrogol 400, polysorbate 80, yellow iron oxide and red iron oxide (strength 75mg/650mg). All excipients used comply with their respective Ph. Eur. monograph, with exception of Opadry, which comply with a satisfactory in-house monograph. Compliance of the products with the general monograph of the Ph. Eur. on the *Products with the risk of TSE* has been demonstrated by the applicant.

The 37.5 mg/325 mg film-coated tablets are yellow-brown, oval; slightly biconvex film coated tablets and packed in PVC/PVdC//Al blisters. The 75 mg/650 mg film-coated tablets are slightly orange oval, biconvex film coated tablets widely scored on the both sides and packed in PVC/PVdC//Al blisters.

The tablets can be divided into equal halves.

As regards dissolution and impurity profile the products are shown to be similar to the reference product. A description and flow chart of the manufacturing method has been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specifications are satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the ICH Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification. Certificates of analysis were also provided for the working standard used.

The container closure system of the products is as follows: PVC/PVdC//Al blisters. Relevant specifications and certificates of analysis have been provided. Satisfactory IR spectrum for identification and heat sealable lacquer on the aluminium foil is provided and confirmation that the primary packaging components are compliant with the Ph. Eur. and the Directive 2002/72/EC was provided.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 2 years for 75 mg/650 mg film-coated tablets and 3 years for 37.5 mg/325 mg film-coated tablets with storage condition of "This medicinal product does not require any special storage conditions" are approved.

The Summary of Product Characteristics, the Patient Information Leaflet and the label text are pharmaceutically acceptable.

II.3 Discussion on chemical, pharmaceutical and biological aspects

The products have been shown to consistently meet the current regulatory requirements with respect to qualitative and quantitative content of the active substance and pharmaceutical form until the end of the approved shelf-lives. The manufacture and the quality standards applied adequately support the safe use and efficacy of the products. There is nothing against granting the marketing authorization for chemical-pharmaceutical points of view.

III. NON-CLINICAL ASPECTS

III.1 Introduction

This application for a marketing authorisation, submitted by Krka d.d. via Decentralised Procedure with Hungary as RMS, concerns an abridged application according to the article 10.1 of the Directive 2001/83/EC (i.e. a generic application, the reference product is Zaldiar from Grünenthal, Germany, authorised since 2002 in the EU) for Doreta 37.5 mg/325 mg film-coated tablets and a hybrid application for s Doreta 75 mg/650 mg film-coated tablets according to Article 10.3 of the Directive.

Doreta film-coated tablets containing of two known substances tramadol hydrochloride and paracetamol, respectively, have been developed for the symptomatic treatment of moderate to severe pain.

Tramadol (as a hydrochloride salt) is a centrally acting analgesic drug with a lasting analgesic effect and a slightly delayed onset of action in comparison with paracetamol.
Paracetamol is a proven effective analgesic and antipyretic with rapid onset of action and has an excellent safety profile.

Rapid onset of paracetamol is combined with the long duration of action of tramadol. The product provides enhanced analgesia because of the three complementary modes of action of the tramadol and paracetamol:

(1) tramadol activates μ-opioid receptors.
(2) tramadol inhibits reuptake of noradrenaline and serotonin.
(3) paracetamol weakly inhibits prostaglandin biosynthesis in CNS.

The maximum recommended daily dose is 2600 mg paracetamol/360 mg tramadol.

III.2 Pharmacology

Tramadol is an opioid analgesic that acts on the central nervous system. Tramadol is pure non selective agonists of the μ, δ, and κ opioid receptors with a higher affinity for the μ receptors. Other mechanisms which contribute to its analgesic effect are inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release. Tramadol has an antitussive effect. Unlike morphine, a broad range of analgesic doses of tramadol has no respiratory depressant effect. Similarly, the gastro-intestinal motility is not modified. The cardiovascular effects are generally slight. The potency of tramadol is considered to be one-tenth to one-sixth that of morphine.

The precise mechanism of the analgesic properties of paracetamol is unknown and may involve central and peripheral effects.

Their combination is positioned as a step II analgesic in the WHO pain ladder and should be utilised accordingly by the physician.

III.3 Pharmacokinetics

Tramadol is administered in racemic form and the [-] and [+] forms of tramadol and its metabolite M1, are detected in the blood. Although tramadol is rapidly absorbed after administration, its absorption is slower (and its half-life longer) than that of paracetamol.

Absorption

Racemic tramadol is rapidly and almost completely absorbed after oral administration. The mean absolute bioavailability of a single 100 mg dose is approximately 75%. After repeated administration, the bioavailability is increased and reaches approximately 90%.

Distribution

Tramadol has a high tissue affinity ($V_{d,\beta}$=203 ± 40 l). It has a plasma protein binding of about 20%.

Paracetamol appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 l/kg. A relative small portion (~20%) of paracetamol is bound to plasma proteins.

Metabolism

Tramadol is extensively metabolized after oral administration. About 30% of the dose is excreted in urine as unchanged drug, whereas 60% of the dose is excreted as metabolites.

Tramadol is metabolised through *O*-demethylation (catalysed by the enzyme CYP2D6) to the metabolite M1, and through *N*-demethylation (catalysed by CYP3A) to the metabolite M2. M1 is further metabolised through N-demethylation and by conjugation with glucuronic acid. The plasma elimination half-life of M1 is 7 hours. The metabolite M1 has analgesic properties and is more potent than the parent drug. The plasma concentrations of M1 are several-fold lower than those of tramadol and the contribution to the clinical effect are unlikely to change on multiple dosing.

Paracetamol is principally metabolized in the liver through two major hepatic routes: glucuronidation and sulphation. The latter route can be rapidly saturated at doses above the therapeutic doses. A small fraction (less than 4%) is metabolized by cytochrome P450 to an active intermediate (the N-acetyl benzoquinoneimine) which, under normal conditions of use, is rapidly detoxified by reduced glutathione and excreted in urine after conjugation to cysteine and mercapturic acid. However, during massive overdose, the quantity of this metabolite is increased.

Elimination

Tramadol and its metabolites are eliminated mainly by the kidneys.

III.4 Toxicology

No new preclinical study has been performed with the tramadol and paracetamol fixed combination to evaluate its carcinogenic or mutagenic effects or its effects on fertility.

No teratogenic effect that can be attributed to the medicine has been observed in the progeny of rats treated orally with the combination tramadol/paracetamol.

The combination tramadol/paracetamol has proven to be embryotoxic and foetotoxic in the rat at materno-toxic dose (50/434 mg/kg tramadol/paracetamol), i.e., 8.3 times the maximum therapeutic dose in man. No teratogenic effect has been observed at this dose. The toxicity to the embryo and the foetus results in a decreased foetal weight and an increase in supernumerary ribs. Lower doses, causing less severe materno-toxic effect (10/87 and 25/217 mg/kg tramadol/paracetamol) did not result in toxic effects in the embryo or the foetus.

Results of standard mutagenecity tests did not reveal a potential genotoxic risk for tramadol in man.

Results of carcinogenicity tests do not suggest a potential risk of tramadol for man.

Animal studies with tramadol revealed, at very high doses, effects on organ development, ossification and neonatal mortality, associated with maternotoxicity. Fertility reproductive performance and development of offspring were unaffected. Tramadol crosses the placenta. No effect on fertility has been observed after oral administration of tramadol up to doses of 50 mg/kg in the male rat and 75 mg/kg in the female rat.

Extensive investigations showed no evidence of a relevant genotoxic risk of paracetamol at therapeutic (i.e. non-toxic) doses.

Long-term studies in rats and mice yielded no evidence of relevant tumorigenic effects at non-hepatotoxic dosages of paracetamol.

Animal studies and extensive human experience to date yield no evidence of reproductive toxicity.

III.5 Ecotoxicity/environmental risk assessment

Evaluation of the potential environmental risk posed by the medicinal products has not been provided. As the applications concern products intended for substitution of the innovator, such an evaluation is deemed unnecessary since no additional amount of tramadol/paracetamol will be introduced in the environment.

III.6 Discussion on the non-clinical aspects

The pharmacodynamic, pharmacokinetic and toxicological properties of both tramadol hydrochloride and paracetamol and of their combination are well known. No new relevant pharmacodynamic, pharmacokinetic and toxicological data regarding the fixed combination were submitted by the applicant. Overview based on literature review is, thus, appropriate.

IV. CLINICAL ASPECTS

IV.1 Introduction

The applications concern the combination of tramadol/paracetamol 37.5 mg/325 mg and 75 mg/650 mg film-coated tablets. To support the application, the applicant has submitted the report of one single dose bioequivalence study with the 37.5 mg/325 mg tablet. The approval of the 75 mg/ 650mg strength is based upon the extrapolation of the results of the bioequivalence study to this strength because all relevant biowaiver criteria of the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) are met.

The precise mechanism of the analgesic properties of paracetamol is unknown and probably involves central and peripheral effects.

Tramadol is an opioid analgesic that acts on the central nervous system as a pure non selective agonist of the μ, δ and κ opioid receptors with a higher affinity for the μ receptors. Other mechanisms also contribute to its analgesic effect: inhibition of neuronal reuptake of noradrenaline and enhancement of serotonin release.

IV.2 Pharmacokinetics

IV.2.1 Literature summary

After a single oral administration of a tramadol/paracetamol (37.5 mg/325 mg) tablet, peak plasma concentrations of 64.3/55.5 ng/ml [(+)-tramadol/(-)-tramadol] and 4.2 μg/ml (paracetamol) are reached after 1.8 h [(+)-tramadol/(-)-tramadol] and 0.9 h (paracetamol) respectively. The mean elimination half-lives $t_{1/2}$ are 5.1/4.7 h [(+)-tramadol/(-)-tramadol] and 2,5 h (paracetamol).

During pharmacokinetic studies in healthy volunteers after single and repeated oral administration of Doreta, no clinical significant change was observed in the kinetic parameters of each active ingredient compared to the parameters of the active ingredients used alone.

After administration of the combination, the oral absorption of paracetamol is rapid and nearly complete and takes place mainly in the small intestine. Peak plasma concentrations of paracetamol are reached in one hour and are not modified by concomitant administration of tramadol.

The oral administration of the tramadol/paracetamol combination with food has no significant effect on the peak plasma concentration or extent of absorption of either tramadol or paracetamol so that it can be taken independently of meal times.

Tramadol and its metabolites are eliminated mainly by the kidneys.

The half-life of paracetamol is approximately 2 to 3 hours in adults. It is shorter in children and slightly longer in the newborn and in cirrhotic patients. Paracetamol is mainly eliminated by dose-dependent formation of glucuro- and sulpho-conjugate derivatives. Less than 9% of paracetamol is excreted unchanged in urine. In renal insufficiency, the half-life of both compounds is prolonged.

IV.2.2 Bioequivalence study

The bioequivalence study with tramadol/paracetamol 37.5 mg / 325mg film coated tablets was a randomized, single-dose, two period, two sequence crossover study conducted under fasting conditions with a 7 days washout period between the doses. The test product Doreta, manufactured by KRKA, was compared with the reference Zaldiar® 37.5 mg / 325film coated tablets (GRUNENTHAL GmbH, Germany). All twenty eight (28) healthy male volunteers who were included in the study completed the trial. Plasma samples were analyzed for tramadol, paracetamol and O- desmethyltramadol by a validated analytical method.

The 90% Confidence Intervals for the test/reference ratios for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} for tramadol, paracetamol and O-desmethyltramadol were all within conventional bioequivalence criteria thus the bioequivalence may be concluded.

The bioequivalence study was stated to be GCP compliant.

The pharmacokinetic results of the bioequivalence study are shown below.

Tramadol

Parameter	Test/Reference	90% confidence intervals
AUC_{0-t}	97.283	92.806 – 101.976
AUC_{0-inf}	98.363	93.669 – 103.292
C_{max}	92.825	86.659 – 99.430

O-Desmethyltramadol

Parameter	Test/Reference	90% confidence intervals
AUC_{0-t}	99.437	96.452 – 102.514
AUC_{0-inf}	99.725	96.605 – 102.947
C_{max}	95.721	91.607 – 100.020

Paracetamol

Parameter	Test/Reference	90% confidence intervals
AUC_{0-t}	97,057	93.935 – 100.282
AUC_{0-inf}	97.309	94.408 – 100.299
C_{max}	103.297	92.272 – 115.639

Conclusion on bioequivalence studies: based on the submitted bioequivalence study Doreta 37.5 mg/325mg film-coated tablets is considered bioequivalent with Zaldiar® 37.5 mg/325mg.

Biowaiver

The results of study with 37.5 mg / 325mg formulation can be extrapolated to other strength 75 / 650 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6.

This biowaiver request is based on the following facts:
a) the two strengths are manufactured by the same manufacturing process,
b) the qualitative composition of the different strengths is the same,
c) the composition of the strengths are dose-proportional,
d) 85% of paracetamol and tramadol of the tablets were dissolved in less than 15 minutes of both the 37.5 mg/325 mg and the 75 mg/650 mg strengths at three different pH values.

Additionally, literature data on tramadol and paracetamol pharmacokinetics show that both active substances have a dose-linear behaviour.

IV.3 Pharmacodynamics

No new data have been submitted. The clinical overview refers to a comprehensive bibliography of 30 references up to year 2007. The clinical on the clinical pharmacology, efficacy and safety is adequate for this type of application.

IV.4 Clinical efficacy

The efficacy of the tramadol/paracetamol combinations has already been demonstrated during the clinical development of the reference product. No new data have been submitted.

IV.5 Clinical safety

The clinical safety of tramadol, paracetamol and their combinations has been well established. The bioequivalence studies did not raise any safety concerns. There was no need for

submission of new data.

IV.6 Discussion on clinical aspects

The products have been shown to be essentially similar and refer to a product approved on the basis of a full application with regard to clinical efficacy/safety data. No further such studies have been submitted or are considered necessary. There is no concern about granting of the marketing authorisation from clinical points of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The present applications concern Doreta 37.5 mg/325 mg and 75 mg/650 mg film-coated tablets. The applicant and the future holder of authorisation is Krka d.d. (Slovenia).

The first application concerning the 37.5 mg/325 mg strength was submitted according to Article 10(1) of Directive 2001/83/EC (generic application). The originator product was Zaldiar 37.5 mg/325 mg (Grunenthal, Germany), authorised for marketing since 2002 in the European Union.

After granting the marketing authorisation, another Decentralised Procedure application concerning the 75 mg/ 650mg strength was submitted. The legal basis of this second application was Article 10(3) of the Community code (hybrid application), line extension.

Later, two repeat-use procedures completed the marketing authorisations involving both strengths.

The products are indicated for the symptomatic treatment of moderate to severe pain for patients whose pain is considered to require a combination of tramadol and paracetamol.

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised. The therapeutic benefit/risk assessment is, therefore, positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Doreta 37.5 mg/325 mg and 75 mg/ 650mg film-coated tablets.

V.1 Conditions for the marketing authorisation

Requirements for specific post-marketing obligations

Not needed.

Pharmacovigilance system

The marketing authorisation holder submitted detailed description of the Pharmacovigilance System intended to be used, which fulfils the requirements and provides adequate evidence that the marketing authorisation holder has the services of qualified persons responsible for pharmacovigilance in all member states concerned and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

No Risk Management Plan, as per the provisions of the EMEA/CHMP/96268/2005 guideline needs not to be submitted with the present generic application. No risk minimization activities additional to those described in the Summary of Product Characteristics are necessary.

Periodic Safety Update Report (PSUR)

The future common renewal date has been agreed with the applicant. Joint PSURS should be submitted for the two strengths provided the different strengths will be discussed separately. A three-year PSUR cycle with the Data Lock Point has been agreed upon.

Legal status

Prescription-only medicine.

V. 2 Summary of Product Characteristics (SmPC)

The SmPC is, from both pharmaceutical and medical aspects, acceptable.

V.3 Package Leaflet and user testing

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. The language used for the purpose of user testing the patient information leaflet was Hungarian.

The results show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

VI. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number HU/H/	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached
New CEP submission, IA	0190/001/IA/001	No	27. 08. 2009	10. 08. 2009	Approval	No
	0190/001/IA/002					
Minor changes in an approved test procedure IA, extension of the shelf-life of the finished product to 3 years, IB	0190/001/IB/003/G		28. 09. 2010	28. 10. 2010	Approval	No
Minor changes in the tablet manufacturing process, IA	0190/001/IA/004	No	17. 05. 2011	16. 06. 2011	Approval	No
	0190/001/IA/006/G		27. 09. 2011	27. 10. 2011		
Tightening of specification limits and addition of a new specification parameter with its corresponding test method, IA	0190/001/IA/007/G	No	08. 11. 2012	08. 12. 2012	Approval	No
	0190/001/IA/008					
	0190/002/007/G					
	0190/002/IA/008					
Grouped Type IB Type IB No. C.l.z: Harmonization of the wording of Product Information texts between the different strengths Type IB No. C.I.3.a: Implementation of agreed wording change(s) for which no new additional data are submitted by the MAH: changes are mentioned in the sections 4.2.	HU/H/0190/01-02/IB/06/G	Yes, SmPC and PIL	18.11.2012	17.12.2012	Approval	No

and 4.5 in reference with the pharmacovigilance recommendations for the risk of convulsion, serotonin syndrome, suicide and posology in the elderly and in patients with renal or hepatic impairment when using tramadol. Doc.Ref.: CMDh/PhVWP/056/2012, July 2012						