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Icelandic Medicines Agency

Public Assessment Report

Scientific discussion

Tramapran
Film-coated tablet
Tramadol 75 mg, Paracetamol 650 mg
Tramadol / Paracetamol

IS/H/0220/001/DC

Date: 13.05.2014

This module reflects the scientific discussion for the approval of Tramapran. The procedure was finalised at 06.05.2014. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Tramapran film-coated tablet 75 mg/650 mg, Tramadol 75 mg and Paracetamol 650 mg, from Zentiva. The product is indicated for symptomatic treatment of moderate to severe pain. A comprehensive description of the indications and posology is given in the SmPC.

This application for Tramapran 75 mg/650 mg film-coated tablets is an application according to article 10.3 of Directive 2001/83/EC. This hybrid application is referring to a so-called reference medicinal product with a Marketing Authorisation granted in a Member State or in the Community, with a change in strength (quantitative change to the active substance(s)).

Tramadol is an opioid analgesic that acts on the central nervous system. Tramadol is a pure non selective agonist 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.

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

The combination of these two compounds is now well recognised for the treatment of moderate to severe pain, since their mechanisms of action are synergistic. The synergism has been documented on preclinical as well as clinical level of evidence. The combination is clearly superior to the analgesia produced by either component alone, while the safety profile is similar to the tolerability of tramadol alone. The fixed dose combination provides an important therapeutic option in the pain treatment allowing spare strong opioid use.

The selected dose of the fixed combination of Tramapran 75 mg /650 mg is identical to two tablets of the original formulation Zaldiar 37.5/325 mg. This dose has been selected to increase patients´ comfort and compliance with the treatment, since the recommended dosing in the originator´s SmPC specifies that initial adult dose is two tablets of the original formulation (i.e. 75/650 mg).
Pharmacotherapeutic group: Tramadol, combinations. ATC code: N02AX52

No discussions were held with CMDh during the procedure.

II. QUALITY ASPECTS

II.1 Introduction

Tramapran is presented as slightly yellowish brown, oblong, biconvex film-coated tablets, half-scored on both sides with dimensions 18 x 9 mm, radius 8 mm. The tablets can be divided into equal doses. Each tablet contains 75 mg of tramadol hydrochloride and 650 mg of paracetamol as active substances.

The tablets contain the following excipients:
Cellulose, microcrystalline (E460)
Povidone K-25 (E1201)
Maize starch
Starch, pregelatinised (maize)
Croscarmellose sodium (E468)
Magnesium stearate (E572)
Lactose monohydrate
Hypromellose
Titanium dioxide (E171)

Triacetin (E1518)
Yellow iron oxide (E172)

The tablets are packaged into white opaque PVC/PVDC/Al blisters.

II.2 Drug Substance

The drug substances are Tramadol hydrochloride and Paracetamol, established active substances of chemical origin.

Tramadol hydrochloride is monographed in the European Pharmacopoeia (n°1681). Tramadol HCl is a white to off-white crystalline powder. It is freely soluble in water and methanol, and slightly soluble in isopropanol. Solubility at different pH´s has been assessed and the substance is considered highly soluble at all the pH tested (from pH 1.00 to pH 6.8). The pKa is 8.3 and pH of 1% aqueous solution is 5.5-7.0.

Paracetamol is monographed in the European Pharmacopoeia (n°0049). Paracetamol is a white crystalline powder and it has no chiral centre in the molecule. It is very slightly soluble in cold water, considerable more soluble in warm water, soluble in methanol, ethanol, DMF, ethylene dichloride, acetone, ethyl acetate, slightly soluble in ether, practically insoluble in petroleum ether, pentane and benzene. Solubility has been analysed at various pH at dose solubility (<250 ml) and found highly soluble at all pH from 1-8. The pH of 1% solution in water is measured between 4.5 and 5.5 and pKa is 9.38.

The active substances specifications include relevant tests and the acceptance limits have been appropriately justified. The analytical methods applied are suitably described and validated as demonstrated with compliance to the Ph.Eur. as CEP for both active substance confirms.

Stability studies have been conducted and the data provided are sufficient to support the proposed retest periods.

II.3 Medicinal Product

The development of the drug product formulation is well described. The excipients used in the product are all standard in the manufacture of film-coated tablets and are compliant with European Pharmacopoeia (or equivalent) requirements.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the finished products specifications are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed in the commercial packaging and data presented support the shelf life claimed in the SPC; 2 years with no special temperature storage condition but store in the original package in order to protect from moisture.

The pharmaceutical quality of Tramapran from Zentiva has been adequately shown.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of active substance and medicinal product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of tramadol and paracetamol are well known. As tramadol and paracetamol are widely used, well-known active substances, the applicant has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

Environmental Risk Assessment (ERA)
Since Tramapran is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

The SmPC text is in line with the SmPC of the reference product Zaldiar, 37.5 mg/325 mg film coated tablets, from Grünenthal GmbH, procedure FR/H/0212/01/MR. The applied product is for a different strength 75 mg/650 mg and consequently the recommended initial dose is 1 tablet instead of 2 tablets for Zaldiar 37.5 mg/325 mg.

IV.2 Pharmacokinetics

Biowaiver
Not applicable.

Bioequivalence study
To support the application, the applicant has submitted as report one (1) bioequivalence study.

The study (no. PRTM-BESD-06-ZNV/12) was an open label, randomised, single dose, 2-period, 2-sequence, crossover bioequivalence study comparing two film-coated tablet formulations of tramadol/paracetamol in equal doses i.e., 1 x 75 mg/650 mg tramadol/paracetamol test formulation vs. 2 x 37.5 mg/325 mg tramadol/paracetmol reference formulation in 42 healthy male and female volunteers under fasting conditions. The study was conducted under standardised conditions. Paracetamol, R-Tramadol and S-Tramadol were measured in human plasma using a validated HPLC/MS/MS method and the study was laboratory-blinded. The results showed that the criteria used to assess bioequivalence between the test and reference formulations were all fulfilled. The test to reference ratio of geometric LSmeans and corresponding 90% confidence interval for the C_{max} and AUC_{0-t} were all within the acceptance range of 80.00 to 125.00% for paracetamol, S-tramadol and R-tramadol. The drugs were generally safe and well tolerated by the subjects included in the study.

Table 1. Pharmacokinetic parameters - Paracetmol (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	39708.472 ±11654.698	40832.257 ±11997.130	10671.719 ±3414.377	1.000 (0.167-3.000)
Reference	40180.707 ±11129.869	41533.658 ±11461.379	11931.715 ±3887.303	0.750 (0.333-4.000)
***Ratio (90% CI)**	98.487% (95.327%-101.750%)	97.972% (95.045%-100.990%)	90.310% (80.010%-101.936%)	-

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

**ln-transformed values*

Table 2. Pharmacokinetic parameters – S-Tramdol (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	938.902±284.274	960.334±285.350	126.683±22.618	1.250 (0.500-4.000)
Reference	926.964±303.976	950.894±309.088	131.709±30.424	1.250 (0.500-3.000)
***Ratio (90% CI)**	101.923% (97.536%-106.508%)	101.706% (97.400%-106.202%)	97.342% (90.855%-104.292%)	-

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

**ln-transformed values*

Table 3. Pharmacokinetic parameters – R-Tramadol (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-t} ng/ml/h	$AUC_{0-\infty}$ ng/ml/h	C_{max} ng/ml	t_{max} h
Test	1060.135±325.601	1085.916±334.144	130.366±23.378	1.250 (0.500-4.000)
Reference	1043.837±329.340	1071.072±339.742	135.100±29.685	1.250 (0.500-2.500)
***Ratio (90% CI)**	102.003% (97.981%-106.190%)	101.862% (97.725%-106.174%)	97.384% (91.317%-103.854%)	-

AUC_{0-t} Area under the plasma concentration curve from administration to last observed concentration at time t.
AUC_{0-72h} can be reported instead of AUC_{0-t}, in studies with sampling period of 72 h, and where the concentration at 72 h is quantifiable. Only for immediate release products
$AUC_{0-\infty}$ Area under the plasma concentration curve extrapolated to infinite time.
$AUC_{0-\infty}$ does not need to be reported when AUC_{0-72h} is reported instead of AUC_{0-t}
C_{max} Maximum plasma concentration
t_{max} Time until Cmax is reached

**ln-transformed values*

Conclusion on bioequivalence study

Based on the submitted bioequivalence study the two Paracetamol/Tramadol formulations, Tramapran 650/75 mg film-coated tablets formulation of Zentiva k.s., Czech Republic (test) and Zaldiar® 325/37.5 mg, two film-coated tablets as a single dose, formulation of Grünenthal, Germany (reference) are considered bioequivalent regarding both the rate and extent of absorption in fasting conditions.

IV.3 Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

IV.4 Clinical efficacy

No new clinical efficacy studies were presented and no such studies are required for this application.

IV.5 Clinical safety

No new clinical safety studies were presented and no such studies are required for this application.

IV.6 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Tramapran 75mg/650 mg.

Summary table of safety concerns as proposed in the RMP:

Important identified risks	**Paracetamol compound**	Acute hepatic failure
		Acute renal failure in the context of overdose
		Severe cutaneous adverse reactions (including Toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS))
		Haemolysis in patients with preexisting severe haemolytic anemia or glucose-6-phosphate-dehydrogenase deficiency
		Blood cell count disorders (agranulocytosis, thrombocytopenia)
	Tramadol compound	Drug dependence and drug abuse
		Withdrawal syndrome
		Convulsions
		Respiratory depression
		Cardiovascular collapse
		Hypoglycaemia
		Central nervous system depression
	Both paracetamol and tramadol	Overdose (accidental and intentional, including self-injurious behavior and suicides)
		Severe allergic reactions (angioedema, anaphylactic shock)
Important potential risks	**Tramadol compound**	Serotoninergic syndrome in case of coadministration with monoamine oxydase (MAO) inhibitors and serotoninergic drugs such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), triptans, tricyclic antidepressants, and mirtazapine
	Both paracetamol and tramadol	Bleeding in case of coadministration with warfarin-like compounds
Missing information	**Tramadol compound**	Use in pregnant and lactating women
		Use in children below the age of 12

The safety concerns are acceptable and the proposed routine pharmacovigilance is considered sufficient to identify and characterise the risks of the product. There are no ongoing or planned studies for the product. The inclusion of appropriate information in the SmPC and PIL is the appropriate risk minimisation measure for this prescription only medicinal product at this point in time.

IV.7 Discussion on the clinical aspects

Tramapran 650/75 mg film-coated tablets from Zentiva is a generic to Zaldiar from Grünenthal. Abridged applications avoid the need for repetitive tests on animals and humans apart from a conduction of a bioequivalence study.

The application contains an adequate review of published clinical data and the bioequivalence has been shown between Tramapran 650/75 mg film-coated tablets from Zentiva and Zaldiar® 325/37.5 mg, two film-coated tablets as a single dose from Grünenthal, Germany.

V. USER CONSULTATION

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 PIL was English. 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. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the risk-benefit ratio for the application for Tramapran film-coated tablet 75 mg/650 mg from Zentiva in the treatment of symptomatic treatment of moderate to severe pain, is considered positive and marketing authorisation can be recommended.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC.

There was no discussion in CMDh.