A randomized, single-site, open-label, 2-way crossover, single-dose Phase I clinical trial to assess the bioequivalence of 2 tablets of a tapentadol 25 mg prolonged-release tablet formulation and 1 tablet of a tapentadol 50 mg prolonged-release tablet formulation in healthy male subjects under fed conditions

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON46632

Source
ToetsingOnline

Brief title
BE Tapentadol

Condition

- Other condition

Synonym
chronic pain in adults

Health condition

chronische pijn bij volwassenen

Research involving
Human

Sponsors and support

Primary sponsor: Grünenthal GmbH
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Bioequivalence, Tapentadol

Outcome measures

Primary outcome

To demonstrate the bioequivalence of 2 tablets of a tapentadol prolongedrelease

(PR) 25 mg tablet formulation and 1 tablet of a tapentadol PR 50 mg tablet

formulation after single oral administration under fed conditions.

Primary pharmacokinetic outcome parameters are AUC (AUC0-inf), AUC0-t, and

Cmax.

Secondary outcome

To assess further pharmacokinetic parameters (tmax, tlag, tlast, MRT, HVD,

CL/f, Vz/f, AUC%extr, t1/2,z, and partial AUC (AUC0-6 h).

To assess the safety and tolerability of both treatments (occurrence of adverse

events).

Study description

Background summary

The drug tapentadol is already approved in many countries throughout the world, including Australia, Canada, the European Union, and the USA. The currently available pharmaceutical forms are prolonged release tablets (with dose strengths from 25 to 250 mg) for the treatment of chronic pain in adults, immediate release tablets (with dose strengths from 50 to 100 mg) and an oral solution for the treatment of acute pain in adults.

Tapentadol is a centrally acting analgesic, meaning that it works on the central nervous system (i.e. in the brain) to reduce pain. This analgesic is characterized by a twofold mechanism of action:
1. Tapentadol works like a painkiller from the class of drugs called opiates (e.g. morphine)
2. Tapentadol prolongs the action of the messenger substance norepinephrine, which influences pain perception among other things.
Tapentadol has been included in List 1 (marketable and prescriptible narcotics) of the Narcotics Act (Opiumwet) and is therefore subject to the provisions of this act.

In this medical-scientific study, two different prolonged release formulations will be compared, one formulation containing 25 mg and the other 50 mg of tapentadol. Both formulations are already approved and are available on the market.

Study objective

The purpose of this study is to investigate how quickly and to what extent two 25 mg prolonged release tapentadol tablets are absorbed and eliminated from the body (this is called pharmacokinetics) when compared to one 50 mg prolonged release tapentadol tablet (this is called bioequivalence).

It will also be investigated how safe both tablets are when administered to healthy volunteers. Tapentadol is no new compound; both tapentadol formulations used in this medical-scientific research are already approved and are available on the market.

Study design

The actual study will consist of 2 periods during which the volunteer will stay in the research center location UMCG for 4 days (3 nights). Between the periods, the volunteer will not be in the research center for 4 to 11 days.

Day 1 is the day of administration of the study compound during each period. In both periods, the volunteer is expected at the research center at 14:00 h in the afternoon prior to the day of administration of the study compound. The volunteer will leave the research center on Day 3 of each period.

Intervention

The volunteer will receive tapentadol as 1 tablet (50 mg, reference formulation) and 2 tablets (25 mg each, test formulation) with 240 milliliter (mL) of tap water.

The volunteer will receive the study compound after a standardized high-fat breakfast. This high-fat breakfast is an extensive breakfast with a fixed composition (2 fried eggs, a portion bacon, fried potatoes, bread and milk). The breakfast has to be started exactly on time and has to be finished completely within 30 minutes. One hour before and after administration of the study compound, the volunteer is not allowed to eat or drink except for the high fat breakfast and the water for intake of the study compound. From 1 hour after administration the volunteer is allowed to drink. Lunch will be served approximately 4.5 hours after administration of the study compound.

Whether the volunteer will receive the reference or the test formulation first will be determined by chance. Half of the volunteers will start with the reference formulation and half with the test formulation. The volunteer will get the other formulation during the second period.

The planning of the study is as follows:

Period 1 (Day 1)
Sequence 1 - 2 x 25 mg Test tablets
Sequence 2 - 1 x 50 mg Reference tablet

7 to 14 days Washout period

Period 2 (Day 1)
Sequence 1 - 1 x 50 mg Reference tablet
Sequence 2 - 2 x 25 mg Test tablets

Study burden and risks

All drugs can potentially cause adverse reactions; the extent to which this occurs differs. The study compound(s) may also have side effects that are still

unknown.

A great deal of knowledge has already been gained about tapentadol in humans from experience in numerous clinical studies in healthy volunteers and in patients and from spontaneous reports in patients treated after marketing authorization. Single doses of up to 300 mg of tapentadol twice daily, and doses of up to 250 mg of prolonged release tapentadol twice daily were found to be safe and tolerable in healthy volunteers. The pharmaceutical formulations used in this medical-scientific research have already been approved and hence, the 50 mg dose of prolonged release tapentadol per treatment period is considered safe for the volunteer.

The most common side effects (occurring in more than 10% of those treated) in medical scientific research on tapentadol tablets with prolonged release of the active substance in the dose range 50 mg to 250 mg twice a day were nausea, dizziness, sleepiness, headaches, and constipation.

In rare cases, treatment with tapentadol can lead to a reduction in the breathing rate, as is known to occur with other opiate class substances.

Tapentadol has not been tested in patients who suffer from seizures. Therefore, the volunteer cannot take part in this study if he suffer from seizures or epilepsy or if he has suffered from them in the past.

The addictiveness of tapentadol has been shown to be similar to other opiate class substances. However, with individual doses of tapentadol given in this study, the likelihood of developing an addiction or withdrawal symptoms is extremely low.

For tapentadol, there have been isolated reports of *serotonin syndrome* when it is taken together with a certain class of antidepressants (selective serotonin reuptake inhibitors). This syndrome is characterized by confusion, abnormal restlessness, fever, sweating, muscle cramps, and diarrhea, and it constitutes a medical emergency. If the volunteer take this type of medication, he cannot take part in this medical-scientific study.

Some drugs that influence messenger substances such as norepinephrine have been reported to increase the risk of suicide in patients who suffer from depression. Although tapentadol strengthens the effect of norepinephrine, as yet, there is no evidence of an increased risk with tapentadol.

As with any medication, allergic reactions (hypersensitivity reactions) may occur after taking tapentadol. These may take the form of redness of the skin, itching, fever, shortness of breath or circulatory problems to the point of life-threatening shock. Suitable medicines and medical treatment methods are available to manage these problems. Medically qualified staff who have been trained to treat medical emergencies will monitor the volunteer during his stay

at the research center. If the volunteer has a known drug allergy or if he suffer from a severe allergic condition, the volunteer is excluded from taking part in this medical-scientific study.

More information about tapentadol can be found in the package leaflet and in an seperate appendix of the subject information document.

The study compound may also have side effects that are still unknown.

Blood draw
The insertion of the needle for drawing blood and/or insertion of the indwelling cannula may cause pain, bleeding or mild infection where the needle goes into your arm. Another possible reaction is feeling dizzy or light-headed. Rare complications during or after a blood draw include fainting, blood clot, infections, inflammation of the vein, scarring of the vein, nerve injuries, and accidental puncture of an artery. The amount of blood sampled during this study does not cause any problems in adults. To compare: a blood donation involves 500 mL of blood being taken each time. Additional blood draws may be necessary for medical reasons.

ECG electrodes
To monitor the heart rate, electrodes (small, plastic patches) will be pasted at specific locations on the chest and abdomen. Prolonged use of these electrodes can cause skin irritation (rash and itching).

Procedures: pain, minor bleeding, bruising, possible infection.

Contacts

Public
Grünenthal GmbH

Zieglerstrasse 6
Aachen 52078
DE
Scientific
Grünenthal GmbH

Zieglerstrasse 6
Aachen 52078
DE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

-Healthy male subjects
-18-55 yrs, inclusive
-BMI: 20.0-28.0 kg/m2, inclusive, with a body weight of no less than 50 kg.
-non-smoking or light-smoking

Exclusion criteria

Suffering from hepatitis B, hepatitis C, cancer or HIV/AIDS. In case of participation in another drug study within 90 days before the start of this study or being a blood donor within 30 days from the start of the study. In case of donating more than 500 ml of blood in the 3 months prior the start of this study.;Evidence or history of alcohol or drug abuse including positive or missing alcohol urine test or
drugs of abuse test.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-05-2018
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Palexia
Generic name:	Tapentadol
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	05-04-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-04-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-08-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-08-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

(Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-003904-39-NL
CCMO	NL65490.056.18