Informed Consent Document (ICD) and Authorization to Use and Disclose Health Information for Research Purposes

Study Title: A double blind, randomized, placebo controlled, parallel group dose-range exploration study of Sativex® in relieving pain in patients with advanced cancer, who experience inadequate analgesia during optimized chronic opioid therapy.

Study Code: GWCA0701

Introduction

You are asked to take part in a research study. Before you decide to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your family doctor if you wish. This document is for you to keep and explains what the study involves. Please ask us if there is anything that is not clear or if you would like more information. Take your time to decide whether or not you wish to take part.

1. What is the purpose of the study?

In this study we wish to find out the effective dose of GW Pharma Ltd's medicine, Sativex®, in relieving pain from advanced cancer and how it compares to a dummy medicine (placebo) that contains no active ingredient. Sativex contains the active ingredients, principally tetrahydrocannabinol (THC) and cannabidiol (CBD). The study will last approximately seven weeks. You will need to come to the study clinic for 4 visits. The study visits will take approximately 2 hours to complete (Visit 3 may be shorter). Once you complete the study, or if you decide to leave the study early, a member of the study staff will contact you for a follow-up telephone call visit two weeks later.

This medicine is currently being tested in the UK and Europe to treat a variety of symptoms and is already licensed in Canada for Multiple Sclerosis (MS) pain and for the relief of pain in patients with advanced cancer. So far approximately 2000 patients have received it. Thirteen studies have also been completed in healthy volunteers. Sativex is an investigational medicine, which means that it has not been approved by the US Food and Drug Administration (FDA), the European regulatory Authority (EMEA), The South African regulatory Authority (MCC), although the FDA has given approval for this particular study to commence.

2. Why have I been chosen?

You have been chosen to take part in this study because you are receiving inadequate relief from your cancer pain despite treatment with opioids. The study will take place at up to 50 centers

across the United States of America, South Africa and other countries as required. Approximately 336 men and women ages 18 and older will take part in this study.

3. Do I have to take part?

It is your choice whether you take part in this study or not. If you do decide to take part you will be asked to sign this consent form in which you agree to the study requirements detailed in this document. You will be given a copy of this signed document to keep for your reference if required.

If you do decide to take part, you are free to leave the study at any time, without giving a reason and no further information relating to your participation in the study will be collected. A decision to withdraw at any time, or a decision not to take part, will have no effect on the usual medical care you receive; you will continue to be treated by your doctor as before.

4. What will happen to me if I take part?

If you agree to join the study and sign the consent form at the back of this document, the study doctor will then ask you questions about your pain, current and recent medication use, and medical history. You will have a medical examination (physical and oral exam) including blood and urine tests, height and weight measurements, vital sign measurements, an electrocardiogram (EKG) and will be asked questions about your medical condition, before the study doctor makes a final decision about whether it is appropriate for you to take part.

If you are female and have not yet been through menopause, a pregnancy test will be performed on the blood samples that you give. This is to minimize the chance of someone who is pregnant entering the study.

The following table lists all the visits you will need to make during the study if the results of your tests show you are suitable for the study and if you still wish to proceed. You will need to be at the research center for approximately two hours for Visits 1, 2, and 4, with Visit 3 being a bit shorter. Also, throughout the study you will be asked to phone a telephone number each day in order to record the severity of your pain, your sleep disruption and your medication usage for the day. There is more information on this in section 5.

Visit	Date	Procedures
1	Start of study	Physical examination, examination of the inside of your mouth, medical history, medication use, blood tests (approximately 1 teaspoon) including pregnancy test (if applicable), urine tests including testing for cannabis, electrocardiogram (EKG - heart tracing), blood pressure and heart rate measurement, height and weight measurement. You will also be told how to record your daily diary information.

Visit	Date	Procedures
2	5 to 14 days after Visit 1 - Start of treatment	Blood pressure and pulse measurement, completion of six questionnaires regarding your pain and your quality of life. You will be asked if you have experienced any side effects or if you have changed any medications. Your diary information will be reviewed and if you are suitable for the study you will be given your study medication at this visit to take home and will be instructed on how to take it.
3	3 weeks after Visit 2	Blood pressure and pulse measurement. You will be asked if you have experienced any side effects or changed any medications. A member of the study staff will collect all study medication and review it along with the diary information. Then you will be given your study medication to take home.
4	5 weeks after Visit 2 - End of treatment	Examination of the inside of your mouth, blood tests (approximately 1 teaspoon) including pregnancy test (if applicable) and urine tests including testing for cannabis will be repeated along with an EKG, blood pressure and pulse measurement, and completion of six questionnaires regarding your pain, and your quality of life. You will be asked if you have experienced any side effects or changed any medications. A member of the study staff will collect all study medication and review it along with the diary information.
5	14 Days after Visit 4	A follow-up phone call from the research center to make sure that everything is okay.

At Visit 2 you will be assigned by chance to one of two groups to receive either Sativex or Placebo (a dummy treatment that contains no active medicine). In addition to the study medication, you will be able to continue to receive your regular painkillers. **You will not be asked to stop taking any of your usual medications.** The study medicine which you will receive, either Sativex or Placebo, is decided at random using a computer, like tossing a coin. You are three times more likely to be assigned to Sativex than placebo; we do not know which treatment you will be given. If we need to know which treatment you are taking we can get this information from GW Pharma Ltd.

A final visit (Visit 4) will be performed at the end of the study (five weeks after visit 2) or earlier if you leave the study for any reason. This is for your safety, to check that there is no change in your condition that has gone unobserved. This will be followed approximately two weeks later with a telephone call to further confirm that you have not experienced any side effects.

5. What do I have to do?

Study Card - You will be given a card stating that you are taking part in this study. **You should carry this at all times for your safety and legal protection.** It should be shown to any other doctors who provide medical care to you while you are taking part in this study. You must return it at the end of the study.

Study Medication – You should take the study medication as instructed by your study doctor. You must bring all the study medication, used and unused to the study visits. We will look at the number of doses you have recorded on the telephone and how much medicine is left. If we

think you have been recording the wrong amounts, or that anyone else has had access to your medication, we may have to ask you to leave the study.

Telephone Diary – During the study you will be asked to phone a telephone number each day and record the severity of your pain, your sleep disruptions and your medication usage during that day. We will show you how to use the telephone to record this information. It is very similar to the procedures used in "telephone banking". If you are not familiar with the telephone system, please ask the site personnel to explain it again. It is very important that you call the telephone number at the same time each day, usually before bed time, to record the information.

Other Medicines - It is very important that you tell us at the beginning of the study which medicines you are taking, both prescription medicines and any you have obtained yourself, including dietary supplements, herbs and vitamins. You should bring all of these medications with you at each study visit.

During the study, you will be allowed to keep taking your own medicines and you should try to keep taking the same medicines, at the same dose. However, if you need to change any of your own medicines, you should tell us of any changes.

If you are currently using cannabis, you must agree to stop at least 30 days prior to your first visit and not use it again throughout the study. If you are found to have been using cannabis, we may ask you to leave the study.

Driving – The study medication may cause side effects such as dizziness, drowsiness and on rare occasions fainting, which may impair your judgment and performance of skilled tasks. You are advised not to drive, operate machinery or engage in any hazardous activity until it is known that the study medication is not affecting your ability to perform these tasks.

Alcohol - Alcohol may interact with the study medicine and produce a much more powerful effect than usual, which can easily cause accidents in the home or elsewhere. You are strongly advised either to avoid alcohol for the duration of the study or to consume it in moderation.

Travel - You may not take your study medication abroad because it is illegal to transport the study medication across international borders. You cannot take part in this study if you plan to take a trip abroad during the period of the study.

6. What is the drug that is being tested?

The active study medicine is called Sativex® and it contains predominantly two cannabinoids, THC and CBD in approximately equal amounts. The placebo is a dummy or inactive treatment that is identical in appearance but it does not contain any active ingredients although it contains colorings and flavorings including Tartrazine.

The study medication may contain the following:

- THC
- CBD
- ethanol
- propylene glycol (this is a chemical compound that is usually colorless, tasteless, odorless, clear oily liquid. It is used together with the ethanol to allow the cannabinoids to become a solution so making it easier to use. It is commonly used in food and cosmetic products and the amount in the study medication is harmless)
- peppermint oil
- colorings:
    - FD&C Yellow No.5 (E102 tartrazine)
    - FD&C Yellow No.6 (E110 sunset yellow)
    - FD&C Red No. 40 (E129 Allura red AC)
    - FD&C Blue No.1 (E133 Brilliant blue FCF)

If you are allergic to any of these you should not take part in this trial. The study medicine contains a very small amount of alcohol.

The study medicines are liquid, contained in a small pump-action spray similar in size and appearance to a breath freshener spray. The medicines are taken gradually by spraying it a number of times into your mouth. We will explain how to take your study medicine.

7. What are the alternatives for treatment?

You do not need to participate in this study to receive treatment for your pain. If the study medicine does not suit you, or you decide not to take part, you may choose to continue taking your regular painkillers. In addition, synthetic cannabinoids such as Marinol® (dronabinol) and Cesamet® (nabilone) are also approved for cancer patients in the USA to treat nausea and vomiting. You should discuss the associated risks and benefits of other treatments with the study doctor.

8. What are the side effects of any treatment received when taking part?

Like all medicines, the active medication may cause side effects in some, but not all patients. The following side effects have been seen with the active medication. They have been categorized by the likelihood of them occurring, and listed in order of frequency i.e. dizziness is the most commonly reported side effect overall. Most of these effects have also been seen with the placebo medication.

- **Very common side effects** which may affect more than one person in every 10 are listed below:

  Dizziness, loss of energy, feeling sick

- **Common side effects** which may affect more than one person in every 100 are listed below (excluding the very common side effects above):

  Discomfort/stinging in the mouth, dry mouth, drowsiness, changed sense of taste, disorientation (includes confusion), feeling drunk, vertigo, poor concentration, weakness, diarrhea, being sick (vomiting), losing touch with reality, depression, irritation in the mouth tiredness, feeling abnormal, feeling of general happiness, increased appetite, loss of balance, blurred vision, mouth ulceration, throat irritation, constipation, abdominal discomfort, forgetfulness, decreased appetite and difficulty in speaking

- **Uncommon side effects** which may affect more than one person in every 1000 are listed below (excluding the common and very common side effects above):

  Falls, hallucination (hearing and/or vision), pain in the tongue, memory loss, thirst, paranoia, anxiety, tooth discoloration, delusional response to a normal perception, fainting, white or red patches in the mouth, areas of skin shedding inside the mouth, misinterpretation of a perception, low blood pressure and mouth discoloration.

To help avoid some of the side effects which may affect your mouth you should vary the area in the mouth where study medication is sprayed. Do not continue spraying onto sore or inflamed areas.

On first taking the study medication some patients have experienced a slight increase in heartbeat, and small decreases in blood pressure and very occasionally patients have fainted after taking the study medication. You should therefore avoid over activity immediately after taking the first few sprays of the medications, or until you are familiar with the effects.

If you experienced: disorientation (or confusion), hallucinations, delusional response to a normal perception or thoughts of committing suicide whilst taking the study medication you should stop taking it and contact us immediately.

In general if unacceptable and unwanted effects occur, do not take your next dose. These effects can be expected to wear off within a few hours, at which point you can start dosing again. If you suffer these or any other effects you should report them to us at your next visit. If you are worried at any time by any of the effects you should contact us using the telephone number provided at the end of this leaflet.

The study medicine should not be taken:

- If you are allergic to any of its contents:
- If you, or any of your immediate family, suffer from known or suspected schizophrenia, or other psychotic illness, or have a history of severe personality or psychiatric disorder.

Care should be taken if you suffer from any of the following: epilepsy or seizures, liver or kidney disease, heart disease or alcoholism. If you know or suspect that any of this applies to you, please contact the study doctor for more information.

When you stop taking the study medications you are not expected to suffer any significant side effects, although some patients have experienced temporary sleep disturbance, a change in emotions or a change in appetite.

9. What are the possible disadvantages and risks of taking part?

The treatment may involve risks to you, which are currently unforeseeable. Every effort will be made to prevent any injury that could result from this research. You understand that complications may arise during the course of the therapy either due to your disease or due to the treatment.

Contraception - if you are sexually active we will ask you to take contraceptive precautions during the study and for three months after your last dose of study medicine unless you are female and are either not of childbearing potential or have been surgically sterilized. It is important that you avoid getting pregnant during the study because, as for most medicines, we do not have enough information to say that this medication is safe in pregnancy. If you are a female and you become pregnant during the study or, if you are male and your partner becomes pregnant you must tell us immediately. If you are a female who is either pregnant or breastfeeding you will not be able to take part in this study.

Insurance - if you have private life or medical insurance you may wish to check with your insurers that being in the study does not affect the conditions of your policy.

Drug testing – if you take the study medication any test for cannabis would be positive. You should therefore inform the tester that you are participating in this study.

New conditions or abnormalities - if we find any condition or abnormality that you are not aware of we will inform you and your family doctor. Your family doctor should arrange any future medical care required.

Blood Samples – the blood samples we ask you to provide, about a teaspoonful each time, may cause some discomfort and/or bruising. You should not donate blood while you are in this study.

10. What are the possible benefits of taking part?

This medicine might be useful in helping to relieve your cancer-related pain. You may get some benefit from the medicine or it is possible that you will get no benefit. The information we obtain from your part in the study will help us to treat future patients more effectively.

11. What if new information becomes available?

Sometimes during the course of a study, new information becomes available about the medicine that is being studied. If this happens, we will tell you about it and discuss with you whether you

want to continue in the study. If you decide to withdraw we will make arrangements for your care to continue. If you decide to continue you will be asked to sign an updated informed consent form. Depending on the new information we, or GW Pharma Ltd, may consider it to be in your best interests to withdraw you from the study. We will explain the reasons and arrange for your care to continue.

12. What happens when the research study stops?

The study medicine will not be available to you if you leave the study. This is because the study medicine is not yet approved by the MCC and therefore cannot be prescribed to you, regardless of whether you feel you have experienced any benefit. We will discuss with you alternative medications and you will continue with your regular medical care.

If the study medicine does not suit you, and you decide to withdraw your consent early, you should tell the study doctor or study staff. We will ask you to return to see us for a withdrawal visit. We will discuss with you alternative medications. In certain circumstances, your participation in the study may be terminated without regard to your consent. For example, if the research is not helping you, if you do not follow the research directions, if you have a serious side effect to the study medicine, or if new information becomes available about the product, which puts your safety and well being at risk. GW Pharma Ltd or other regulatory agencies may also stop the study for any reason.

13. What if something goes wrong?

Every effort to prevent injury that could result from this trial will be taken by your doctor and the study sponsor (GW Pharma Ltd). However, should any injury or health problems occur as a direct result of the trial, GW Pharma Ltd may provide compensation. Compensation will be determined according to the guidelines laid down by the Association of the British Pharmaceutical Industry. A copy of these guidelines is available to you on request.

It is important to note that nothing said in this consent form alters your legal rights to recover damages. However, if any physical injury should occur to you which is determined by your study doctor and GW Pharma Ltd (the sponsor company) to be a direct result of your participation in this study as outlined by the study plan, payment for medical treatment (or services) of the injury that are not covered by the state/ federal governmental health care plans or private medical insurance (if any), may be available through GW Pharma Ltd. While GW Pharma Ltd makes no commitment to provide compensation beyond this point, you retain all your legal rights to pursue other possible avenues of compensation. By signing this form you are not giving up any of your legal rights.

Every effort will be made to prevent any injury that could result from this research. You understand that complications may arise during the course of the therapy, either due to your disease or due to the treatment.

In case of an injury or illness from participating in this study, you will receive the appropriate medical treatment for that injury. You do not give up any of your legal rights by signing this form.

If you believe that you have a research-related injury, further information concerning the availability of compensation or treatment can be obtained from us using the telephone number provided at the end of the document.

14. Will there be costs for participating?

GW Pharma Ltd will refund reasonable travel costs from being in this study. If you think there may be problems with travel, please discuss them with us before joining the study.

GW Pharma Ltd will pay for the costs of the study medicine and all study-related procedures as detailed in this document. However, the costs of your regular medications (including your painkillers or rescue medications) will be your responsibility.

15. Will I be paid for participating?

No, you will not be paid for your participation in this study.

16. Will my taking part in this study be kept confidential?

GW Pharma Ltd, the study doctors and nurses and other personnel involved in running this study are committed to respecting your privacy, and promise to maintain the confidentiality of personal health information and use it only as set out below. The term "Personal Health Information" means any information that can be used to identify you, including your name or initials, date of birth/age, gender, ethnic origin (if required for purposes of the study) and medical and health related information such as blood tests, the results of physical examinations, medical history and hospital records.

In the context of this study, your personal information will only be collected, used and disclosed for the purposes of this study as explained in this form, including research, the administration of this study and for your safety, and as required or permitted by law.

Study records that identify you will be kept confidential as required by law. By signing this consent form, you agree to allow the study doctors and nurses and other personnel involved in running this study to use and disclose health information about you to the Institutional Review Board (IRB), the sponsor (GW Pharma Ltd), representatives of the sponsor assisting with the research (such as the contract research organization (Quintiles, Inc, RDDA, etc.), the study monitors, auditor, and project manager), central laboratory and government agencies where permitted or required by law (such as the Food and Drug Administration (FDA) and the United States Department of Health and Human Services, the MCC).

Health information about you will be used and disclosed for medical, statistical, and regulatory purposes related to the research. The people listed above may further disclose this health

information about you. If disclosed by them, the information may no longer be covered by the federal or state privacy regulations.

Your identity, including personal information such as your name, date of birth / age and gender will be known by the study doctors and nurses and other personnel involved in running this study. It will also be known to representatives of GW Pharma Ltd who need to review your medical records at the study site to make sure that the study has been carried out according to applicable laws and regulations. It may also be known to representatives of GW Pharma Ltd's affiliated companies. The FDA, MCC and the IRB (an independent committee that reviewed the ethical aspects of this study to help protect the rights and welfare of the study participants), may also need to review your medical records for the same reason. However, your name will never be collected or used in any other way.

When the results of the study data and copies of your relevant medical records are provided to GW Pharma Ltd, they will not include your name.

Your personal information such as your medical and health information will also be used to confirm your eligibility for the study to assess the results of the study, for purposes of safety and to meet applicable legal and regulatory requirements.

All of your personal information, except for your name, will be collected by GW Pharma Ltd and stored for 25 years as required by law. This information may also be provided to other GW Pharma Ltd affiliated companies or companies hired by GW Pharma Ltd to process or store the study data. It may also be provided to the FDA, MCC, as required by law, and possibly to government agencies in other countries, as required by foreign law. Your personal information may also be provided to the IRB that approved the study. However, GW Pharma Ltd and its representatives and affiliated companies will make every effort as required by law to protect your personal information from being disclosed to any unauthorized parties.

Your study data and personal information will be included in the study results. If the results are presented or published in the medical literature, you will never be identified by name.

If your participation in the study is stopped early for any reason, all of your study data and any personal information collected for the purposes of the study to the date of withdrawal may continue to be used, processed, stored, reported and disclosed as described above, but no new information will be collected.

While every effort will be made to protect the privacy of your information, absolute confidentiality cannot be guaranteed. This does not limit the duty of the researchers and others to protect your privacy. You have a right to check your health records and request changes if the information is not correct.

If you give permission, your regular treating doctor will be told about your taking part in this study, unless you do not give permission.

17. Authorization for Use and Disclosure of Health Information for Research Purposes

By signing this consent form, you authorize the use of the health information about you as described above. This Authorization will not have an expiration date. However, you have the right to revoke this Authorization, in writing, at any time by sending written notification to <<Name of the Principal Investigator at the Site OR Name of the Researchers' Privacy Contact (identify this person as the privacy contact)>> at <<mailing address of site. May also include email address>>.

If you revoke your Authorization for Use and Disclosure of Health Information for Research Purposes, you will be discontinued from the research. If you revoke this Authorization, the Researchers may still use and disclose the health information that has already been obtained to maintain the reliability of the research. You cannot be denied medical treatment because you do not give this Authorization. However, you will not be allowed to participate in this research study. You are allowed to see the information about you in the research study records, if you ask to do so, however, to protect the reliability of the research information, you will not have access to this information about you until the end of the study.

18. What will happen to the results of the research study?

At the end of the study the results will be detailed in a report and may be published in a medical journal or presented at a medical conference. You will not be identified in any of these. We will be able to provide you with a summary of the results if you wish.

19. Who is organizing and funding the research?

This study is funded by GW Pharma Ltd who will pay <<insert name of hospital/surgery/ doctor>> for including you in this study.

20. Who has reviewed this study and contact information?

This study has been reviewed by the IRB - an independent committee that reviewed the ethical aspects of this study to help protect the rights and welfare of study participants and . the MCC has also reviewed the details of the study protocol and has determined that it is safe to conduct the study.

If you have any questions about your rights as a research subject, or complaints regarding this research study, you should call:

SAMA Research Ethics Committee
Castle Walk Corporate Park,
Block F, Nossob Street,
Erasmuskloof Ext.3,
Pretoria, 0153
Tel: 012 481 2000
Fax: 012 481 2100

If you have questions about this trial you should first discuss them with your study doctor or the ethics committee (contact details as provided on this document). After you have consulted your study doctor or the ethics committee and if they have not provided you with answers to your satisfaction, you should write to the Medicines Control Council (MCC) South Africa at:

The Registrar
SA Medicines Control Council
Department of Health
Private Bag X828
PRETORIA
0001
Fax: (012) 323-4474
E-mail: labusa@health.gov.za

You may ask questions about this study at any time. If you feel that you have experienced an adverse reaction to the study medicine or procedures, or if you feel unusually unwell during the study, you should contact us. <<Give contact name (Investigator and research nurse), telephone (office and emergency numbers), and address. >>

If you have any questions about the informed consent process or your rights as a research patient or you require any further information then you should contact us using the above details.

In case of an emergency, please go to the nearest hospital emergency department.

Thank you for taking the time to read this information.

21. Signatures

Investigator: <<name>>

Study Title: GWCA0701 - A double blind, randomized, placebo controlled, parallel group dose-range exploration study of Sativex® in relieving pain in patients with advanced cancer, who experience inadequate analgesia during optimized chronic opioid therapy.

1. I confirm that I have read and understood the patient information in this consent document, version 27 March 2008 for the above study and have had the opportunity to ask questions..... ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected..... ☐
3. I understand that responsible individuals on behalf of GW Pharma Ltd or the regulatory authorities may look at sections of my medical notes where it is relevant to my taking part in this study. I give permission for these individuals to have access to my records..... ☐

4. I am aware that the use of the study medication in this study may impair my judgment and ability to perform skilled tasks. I understand that I should not drive, operate heavy machinery or engage in any hazardous activity until it is known that the study medication is not affecting my ability to do so. I understand that the medicine may interact with alcohol and other drugs and increase their effects. I confirm that the study team has given me this advice based on the current information available to them. If I decide to drive, operate machinery, or engage in any hazardous activity then the study team cannot accept responsibility, financial or otherwise, for any accidents arising out of my actions. ☐

5. I agree to the transfer of my personal information, including sensitive information, collected during this study, to countries inside or outside the United States of America for review, processing and/or storage. I am aware that this may include transfer of my personal data to countries that may not comply with the various state and federal confidentiality laws, e.g. The Health Information Portability and Accountability Act (HIPAA). ☐

6. I agree that my physician can be contacted about my participation in this clinical trial ☐

7. I agree to take part in the above study and to comply with the requirements to the best of my ability ☐

8. I understand that it is illegal under federal law to use cannabis or cannabis-based medicine, other than the medicine in this study, even if it has been recommended to me by a doctor. ☐

Name of Patient (print)	Signature	Date
Name of Investigator taking consent (print)	Signature	Date
Name of research nurse (print) involved in consent process	Signature	Date
Name of legal representative (print)	Signature	Date
Relationship to patient		