CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-981

PROPRIETARY NAME REVIEW(S)

Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
HFD-420; WO22; Mail Stop 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME, LABEL AND LABELING REVIEW

DATE OF REVIEW: October 5, 2007

NDA #: 20-981

NAME OF DRUG: **Oral Hycamtin®**
(Topotecan) Capsules
0.25 mg and 1 mg

NDA SPONSOR: GlaxoSmithKline

NOTE: This review contains proprietary and confidential information that should not be released to the public.

I. INTRODUCTION

This consult was written in response to a request from the Division of Drug Oncology Products for an assessment of the proprietary name, Oral Hycamtin, regarding potential name confusion with other proprietary or established drug names. Hycamtin is currently marketed in the injectable form. The name, Hycamtin, was not reviewed by DMETS since the New Drug Application was approved prior to establishment of DMETS. Additionally, the sponsor submitted container labels and carton and insert labeling for review and comment at this time.

PRODUCT INFORMATION

Oral Hycamtin (topotecan) is indicated for treatment of patients with relapsed small cell lung cancer. The recommended dose is 2.3 mg/m^2/day orally once daily for 5 consecutive days repeated every 21 days. For patients who experience grade 3 or 4 neutropenia or thrombocytopenia, the Oral Hycamtin dose should be reduced by 0.4 mg/m^2/day (to [redacted] mg/m^2/day) for subsequent courses. Oral Hycamtin is available in 0.25 mg and 1 mg capsules. b(4)

Hycamtin is already available as an injectable dosage form of the proposed product. The recommended dose for the injectable Hycamtin for ovarian and small cell lung cancers is 1.5 mg/m^2 by intravenous infusion over 30 minutes daily for 5 consecutive days, every 21 days. In the event of neutropenia and thrombocytopenia, this dose should be reduced by 0.25 mg/m^2 (to 1.25 mg/m^2) for subsequent courses. For cervical cancer, the recommended dose is 0.75 mg/m^2 by intravenous infusion over 30 minutes daily on days 1, 2 and 3, followed by cisplatin 50 mg/m^2 by intravenous infusion on day 1, repeated every 21 days. Hycamtin dose should be reduced by 20% for subsequent courses in the event of febrile neutropenia.

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of the internet, several standard published drug product reference texts[1,2] as well as several FDA databases[3,4] for existing drug names which sound-alike or look-alike to Oral Hycamtin to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. The Saegis[6] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name. Following completion of these initial components, an overall risk assessment is conducted that does not evaluate the name alone. The assessment considers the findings from above and more importantly integrates post-marketing experience in assessing the risk of name confusion, product label/labeling, and product packaging. Because it is the product that is inserted into the complex and unpredictable U.S. healthcare environment, all product characteristics of a drug must be considered in the overall safety evaluator risk assessment.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Oral Hycamtin. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proposed proprietary name, Oral Hycamtin, acceptable from a promotional perspective.

2. The Expert Panel identified a total of 10 proprietary names that were thought to have potential for confusion with Oral Hycamtin. The Expert Panel also noted safety concerns regarding the route of administration in the name and the potential overlapping dose with the intravenous Hycamtin.

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[1] MICROMEDEX Integrated Index, 2007, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-07, and the electronic online version of the FDA Orange Book.

[4] Phonetic and Orthographic Computer Analysis (POCA)

[5] WWW location http://www.uspto.gov/tmdb/index.html.

[6] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Oral Hycamtin with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. Two inpatient orders were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Oral Hycamtin (see below). These orders were optically scanned and delivered to a random sample of the participating health professionals via e-mail. In addition, the inpatient order was recorded on voice mail. The voice mail message was then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal order, the participants sent their interpretations of the orders via e-mail to the medication error staff in DMETS.

HANDWRITTEN MEDICATION ORDERS	VERBAL ORDER
Inpatient Order: Oral Hycamtin (2.3/m²) 4mg po qd x 5days	Oral Hycamtin 4 mg orally daily for 5 days
Inpatient Order: Oral Hycamtin 4 mg po daily x 5 days (2.3 mg/m	

2. Results:

Three respondents from the written studies left out the "Oral" in the name and misinterpreted the proposed name as "Hycamten" or "Hycamtin", the already marketed intravenous formulation of the proposed product (see discussion in Section II.C.1). See appendix A for the complete listing of interpretations from the verbal and written studies.

C. SAFETY EVALUATOR RISK ASSESSMENT

The primary safety concerns from a medication errors perspective identified and evaluated in the review of Oral Hycamtin concern the risk of medication errors resulting from the extension of the Hycamtin product line, potential for name confusion with the proposed proprietary name, Oral Hycamtin, and inclusion of the route of administration in the name.

1. Extension of the Existing Product Line

Oral Hycamtin will be introduced into the Hycamtin product line. Currently, an injectable form of topotecan is available as Hycamtin. See Table 1 on page 3.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel for Oral Hycamtin			
Product Name	Established name; Dosage form(s)	Usual adult dose	Other
Oral Hycamtin	Topotecan; Capsules: 0.25 mg, 1 mg	2.3 mg/m²/day for 5 consecutive days, repeated every 21 days	
Hycamtin	Topotecan Injectable: 4 mg/vial	**Ovarian and Small cell lung cancer:** 1.5 mg/m²/day over 30 min IV infusion for 5 consecutive days, repeated every 21 days **Cervical cancer:** 0.75 mg/m²/day over 30 min IV infusion on days 1-3, repeated every 21 days	LA/SA
*Frequently used, not all-inclusive. **LA (look-alike), SA (sound-alike)			

Post-marketing experience has shown that extension of a product can result in medication errors especially when there is a knowledge deficit with respect to the introduction of the new formulation. In one medication error study evaluating 862 prescribing errors[7], the most common type of prescribing error involved the wrong route of administration. The common prescribing errors were orders where a drug was given orally instead of by the correct intravenous route and orders where a drug was given intravenously instead of by the correct oral route. The most commonly assigned medication characteristic contributing to prescribing errors was the common use of a drug by multiple routes of administration. Similarly, the most common factor enabling the prescribing errors to be carried out as ordered was the availability of a drug in multiple dosage forms.

Placing the route of administration "Oral" on the label may not sufficiently minimize the risk of error inherent to the Hycamtin product line extension for several reasons. First, with the introduction of the proposed product, errors can be anticipated due to omission of the route ("Oral") preceding the root name, Hycamtin, and many overlapping product characteristics such as same established name (topotecan), indication for use (small cell lung cancer), and potential overlapping total dose. Most concerning is if confusion were to occurr between the two formulations, the doses differ which could increase the risk of adverse events.

a. Omission of the Route of Administration in Name

The proposed proprietary name, Oral Hycamtin, contains the route of administration (i.e. oral) in the name. DMETS recognizes the inclusion of the route of administration is the sponsor's attempt to distinguish the proposed product from the already existing intravenous formulation of Hycamtin. However, DMETS believes that the addition of "oral" in the proprietary name will not have an impact in distinguishing the oral and intravenous formulations. Modifiers usually reflect difference in dosage form rather than route of administration. Precribers will likely omit "Oral" when prescribing Oral Hycamtin because oral is not generally used in any tradename. This type of prescribing error (omission) has been demonstrated in postmarketing experience with drug name modifiers.

[7] Lesar T. Medication Prescribing Errors Involving the Route of Administration. *Hosp Pharm.* 2006; 41: 1053-1066.

Additionally, having the route of administration in the proprietary name is duplicative as the route would be usually included on prescription orders as part of the directions for use (i.e. PO). This redundancy further increases the likelihood for prescribers to omit the word "Oral" from the proprietary name.

The potential for this type of error was confirmed by our written prescription analysis studies. Three respondents left out the "Oral" in the name and misinterpreted the proposed name as "Hycamten" or "Hycamtin". Therefore, DMETS does not believe the inclusion of the route of administration "Oral" in the name will help minimize confusion between the intravenous and oral form of Hycamtin.

b. Potential Overdose with Intravenous Hycamtin

We recognize the potential for overdose if the oral and intravenous products are confused for one another. The dosing directions (daily for 5 consecutive days every 21 days) are the same for both dosage forms for the indication of small cell lung cancer. However, for this indication of use, the dose differs between the two dosage forms [2.3 mg/m^2 (oral) vs. 1.5 mg/m^2 (intravenous)] and may represent a potential source of error. Specifically, the differences may increase the risk for Hycamtin to be prescribed at incorrect doses. Additionally, the calculated total dose for both dosage forms can potentially overlap especially if the patient is receiving a reduced recommended dose of Oral Hycamtin (1.9 mg/m^2). This potential overlap can contribute to confusion between intravenous and oral route if the route of administration is missing from the prescription order or the pharmacist overlooks the route on the order form. For example, an order for "Hycamtin 3.25 mg for 5 days, every 21 days" can be applied to both intravenous and oral Hycamtin. This confusion can result in overdose of intravenous Hycamtin. Since Hycamtin is a cytotoxic chemotherapy product, the potential overdose can result in serious injury, harm or death. Although Oral Hycamtin may be more likely to be used in the outpatient setting, the potential for confusion with intravenous form can be problematic in the inpatient setting where both intravenous and oral formulations may be used.

Another concern is if the patient is receiving combination chemotherapy with cisplatin. Although combination therapy is not indicated for Oral Hycamtin, it was studied in clinical trials with cisplatin. During the study, the regimen for Oral Hycamtin was 1.7 mg/m^2/day for 5 days with intravenous cisplatin 60 mg/m^2 on day 5 for small cell lung cancer. This off-label regimen can be confused with the approved combination therapy with intravenous Hycamtin (0.75 mg/m^2/day) and cisplatin (50 mg/m^2 on day 1) for cervical cancer. The difference of cisplatin dose between the different dosage forms of Hycamtin can result in incorrect dosing of cisplatin.

Given our concerns with the potential for confusion between the Hycamtin products, one option DMETS considered was to have the sponsor propose a different tradename for the oral Hycamtin. However, there are risks associated with the use of two different proprietary names for the same active ingredient from the same manufacturer. The primary concerns are that the use of dual tradenames may result in concomitant administration of both products or the administration to a

patient with a documented allergy, hypersensitivity, or intolerance to the active ingredient if practitioners are unaware that both products contain the same active ingredient. Although there is a potential for dosing errors because the oral dose will differ from the existing intravenous Hycamtin, DMETS believes that a greater risk of error may be introduced with the use of dual tradenames. Therefore, DMETS does not recommend the use of dual tradenames.

We recognize that errors may still occur if the products are labeled with the same name but the risk of concomitant dosing outweighs the risk of potential dosing errors. Therefore, to minimize the risk of dosing errors, an educational campaign to alert the healthcare practitioners about the existence of the oral formulation may help. However, even with such education, we foresee errors to occur.

2. Oral Hycamtin Name Evaluation

In reviewing the proprietary name, DMETS also reviewed the name, Hycamtin, concurrently with Oral Hycamtin since DMETS objects to the inclusion of the route of administration in the name. The intent of this undertaking was to generate a robust proprietary name risk assessment that would enable DMETS to identify concerns with either presentation, and thus enable the sponsor to delete the "Oral" from the proprietary name and use the name "Hycamtin" without having to resubmit the proprietary name for evaluation.

The following ten names were identified to have potential similarity in appearance and sound to Oral Hycamtin or Hycamtin: OxyContin, Macrodantin, Hycodan, [redacted] b(4)
Hygroton, Hycomine, Hyamine, [redacted]***, Akineton, and Hycamtin.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that Oral Hycamtin could be misinterpreted as "Hycamtin" since three respondents from the written studies left out the "Oral" in the name. Although there are limitations to the predictive value of these studies, primarily due to sample size, we have identified safety concerns due to the positive interpretation with this drug product. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population.

In the initial analysis of these ten names, it was determined that Hycamtin posed the greatest risk for confusion as discussed in Section II.C.1. The remaining nine names: OxyContin, Macrodantin, Hycodan, [redacted], Hygroton, Hycomine, Hyamine, [redacted] b(4)
***, and Akineton were evaluated and determined to not pose a signification safety risk for the following reasons.

- All of the nine names lack of convincing look-alike and/or sound-alike similarities to Oral Hycamtin.
- All of the nine products do not share product commonalities such as indication for use, product strength, usual dosage, route of administration, frequency of administration, and dosage form.
- Hycomine is a discontinued product and generics are not available.

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- [redacted]
- [redacted] is registered as [redacted] but limited information was available. The name could not be found in common sources such as Drugs@FDA, Facts and Comparison and Orange Book. b(4)

Thus, for the reasons outlined in the Section II.C.1 above, DMETS does not object to the use of the proprietary name "Hycamtin" for this product but object to the use of the proposed name "Oral Hycamtin".

III. COMMENTS TO THE SPONSOR

DMETS does not recommend the use of the proprietary name, Oral Hycamtin. We specifically object to the use of "Oral" in the name. We believe this oral formulation could be managed under the name, Hycamtin, which we find acceptable.

The primary safety concerns from a medication errors perspective identified and evaluated in the review of Oral Hycamtin concern the risk of medication errors resulting from the extension of the Hycamtin product line, potential for name confusion with the proposed proprietary name, Oral Hycamtin, and inclusion of the route of administration in the name. DMETS has also identified several areas of possible improvement with the labels and labeling which might minimize potential user error.

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both intravenous and oral Hycamtin. This confusion can result in overdose of intravenous Hycamtin. Since Hycamtin is a cytotoxic chemotherapy product, the potential overdose can result in serious injury, harm or death. Although Oral Hycamtin may be more likely to be used in the outpatient setting, the potential for confusion with intravenous form can be problematic in the inpatient setting where both intravenous and oral formulations may be used.

Another concern is if the patient is receiving combination chemotherapy with cisplatin. Although combination therapy is not indicated for Oral Hycamtin, it was studied in clinical trials with cisplatin. During the study, the regimen for Oral Hycamtin was 1.7 mg/m^2/day for 5 days with intravenous cisplatin 60 mg/m^2 on day 5 for small cell lung cancer. This off-label regimen can be confused with the approved combination therapy with intravenous Hycamtin (0.75 mg/m^2/day) and cisplatin (50 mg/m^2 on day 1) for cervical cancer. The difference of cisplatin dose between the different dosage forms of Hycamtin can result in incorrect dosing of cisplatin.

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We recognize that errors may still occur if the products are labeled with the same name but the risk of concomitant dosing outweighs the risk of potential dosing errors. Therefore, to minimize the risk of dosing errors, an educational campaign to alert the healthcare practitioners about the existence of the oral formulation may help. However, even with such education, we foresee errors to occur.

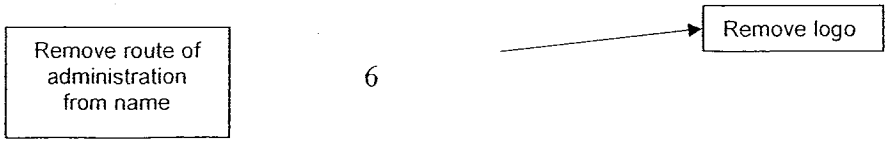
B. Label and Labeling Safety Issues

In the review of the container labels, carton and insert labeling of Oral Hycamtin, DMETS has attempted to focus on safety issue relating to potential medication errors. DMETS has identified several areas of possible improvement which might minimize potential user error.

1. General Comments

   a. Remove the route of administration (i.e. oral) from the proprietary name.

   b. Remove the blue circle surrounding the name because this interferes with the proprietary name and decreases the prominence of the name. Additionally, this is distracting for the reader.



b(4)

2. Container Labels

   a. See General Comments 1a and 1b.

3. Carton Labeling

   a. See General Comments 1a and 1b.

   b. The product strength and the net quantity are presented too close together. The product strength and the net quantity on the proposed label are in close proximity to each other and could lead to confusion. The strength should be relocated to immediately follow the established name and dosage form.

4. Insert Labeling

   a. DMETS notes that vomiting is one of the non-hematologic adverse events seen in the clinical trials. However, DMETS is unable to find any recommendations or guidance for the patient or prescriber on what to do in the event the patient vomits the Oral Hycamtin dose. The Sponsor should add a statement and provide recommendations in the DOSAGE AND ADMINISTRATION and PATIENT INFORMATION sections.

   b. Under DOSAGE AND ADMINSTRATION section, the dosing instructions do not advise practitioners how to round the calculated dose if it is not exactly in increments of 0.25 mg (the lowest strength of capsules available). Please include this information in this section.

   c. Under HOW SUPPLIED section, please justify supplying the bottles with a net

b(4)

Appendix A

Oral Hycamtin Prescription Study Results

Written Inpatient 1	Written Inpatient 2	Voice
Oral Hycamtin	Oral Hycantin	Oral Hycampton
Oral Hycarntin	Hycamtin	Oral Hykeptin
Oral Hycamtin	Oral Hycamtin	Oral Hycamphen
Oral Hycamtin	Oral Hycamtin	Oral Hycamtin
ORAL HYCARNTIN	Oral Hycamtin	Oral Hykemtin
Hycamtin	Oral Hyramtin	
Oral Hycarntiu	Oral Hycamtin	
Oral Hycamtin	Oral Hycamtin	
Oral Hycamtin	Oral Hycamtin	
Hycamptin	Oral Hycamtin	
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Judy Park
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DRUG SAFETY OFFICE REVIEWER

Kellie Taylor
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DRUG SAFETY OFFICE REVIEWER

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10/5/2007 04:15:27 PM
DRUG SAFETY OFFICE REVIEWER

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	September 20, 2007
To:	Robert Justice, M.D., Director Division of Drug Oncology Products
Thru:	Toni Piazza-Hepp, PharmD, Deputy Director Division of Surveillance, Research and Epidemiology
From:	Sharon R. Mills, BSN, RN, CCRP Patient Product Information Specialist Division of Surveillance, Research and Communication Support
Subject:	DSRCS Review of Patient Labeling Materials (Patient Package Insert)
Drug Name(s):	Oral HYCAMTIN (topotecan) Capsules
Application Type/Number:	N20-981
Applicant/sponsor:	GlaxoSmithKline
OSE RCM #:	2007-1279

1 INTRODUCTION

HYCAMTIN (topotecan hydrochloride) For Injection, For Intravenous Use, was granted a priority review and received original approval on May 28, 1996 under NDA# 20-671, for the new molecular entity topotecan hydrochloride. GlaxoSmithKline submitted NDA# 20-981 on April 11, 2007, seeking approval for Oral HYCAMTIN (topotecan) Capsules in 0.25 mg and 1 mg. indicated "for the treatment of patients with relapsed small cell lung cancer." This application was granted a priority review. In response to Agency email communication regarding PLR formatting comments dated June 22, 2007, the Sponsor submitted revised labeling on July 11, 2007. The review division further revised the labeling on September 13, 2007.

2 MATERIAL REVIEWED

Revised DRAFT Professional Information (PI) dated September 13, 2007, and proposed Patient Labeling in the form of a Patient Package Insert (PPI) appended as section 17.4 FDA-Approved Patient Labeling.

3 DISCUSSION

See the attached document (marked up and clean copies for our suggested changes to the draft Patient Package Insert (PPI) for Oral HYCAMTIN. Comments to the review division are ***bolded, underlined and italicized.*** We recommend using the clean copy as the working document.

The purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medicines. We have simplified the wording where possible, made it consistent with the Professional Information (PI) and removed unnecessary information. These recommended changes are consistent with research to improve risk communication to a broad range of audiences of varying educational backgrounds including those with lower literacy levels.

CONCLUSIONS AND RECOMMENDATIONS

- A PPI for Oral HYCAMTIN is voluntary. Unless Oral HYCAMTIN is dispensed in unit-of-use packaging with the PPI enclosed, it is highly unlikely that patients will receive the PPI.
- The draft PPI submitted by the Sponsor has a Flesch Kincaid grade level of 6.9 and a Flesch Reading Ease score of 64.3. To enhance comprehension, patient materials should be written at a 6^{th} to 8^{th} grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8^{th} grade reading level). The reading scores as submitted by the sponsor are acceptable. However, we have made changes as described above under *Discussion.*
- We have added the section, "What is the most important information I should know about Oral HYCAMTIN?" in order to convey important safety information to patients from the

PI boxed warning as well as Warnings and Precautions (section 5), subsections 5.1 Bone Marrow Suppression and 5.2 Diarrhea.

- The PI lists fatigue, asthenia and malaise as adverse reactions. Drowsiness and sleepiness do not appear in the PI. This should be clarified. If these are adverse reactions, they should appropriately appear in the PI; otherwise they should be deleted from the PPI. Also, consider adding the instruction not to drive, use heavy tools or operate machinery, to PI section 17 Patient Counseling Information.
- Serious side effects should be listed first and address the boxed warning and Warnings and Precautions section of the PI. The serious side effects of Oral HYCAMTIN must not be minimized.
- Section 16 of the PI, How Supplied/Storage and Handling, states "Procedures for proper handling and disposal of anticancer drugs should be used." The sponsor should also include instructions for handling and safe disposal by patients in the PPI.

Please let us know if you have any questions.

9 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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Sharon Mills
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MEDICAL OFFICER
For Toni Piazza-Hepp