

Safety and Efficacy Issues

Genetic basis of adverse drug events

United States of America — The first data offering health care professionals a better look into the genetic basis of certain types of adverse drug events has been released by the Food and Drug Administration (FDA) and the International Serious Adverse Event Consortium (SAEC). Data are focused on the genetics associated with drug-induced serious skin rashes, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, and help better predict an individual's risk of developing these reactions.

Both skin conditions appear as allergic-like skin reactions associated with blistering and peeling, and are considered life-threatening. Medications causing these serious allergic reactions should be discontinued. If such signs and symptoms are not quickly recognized, these reactions can be fatal.

The SAEC is a non-profit partnership of pharmaceutical companies, the Wellcome Trust, and academic institutions focused on research relating to the genetics of drug-induced serious adverse events.

Researchers who enter into a data use agreement can obtain free access to the data to generate custom data inquiries and obtain immediate results on the genetic basis of adverse drug events.

References

1. *FDA News*, 10 February 2009. www.fda.gov
2. International Serious Adverse Event Consortium at <http://www.saeconsortium.org>

Anaesthetic infusion with pain pumps: articular chondrolysis

Canada — Postoperative pain pumps are infusion devices designed to continuously deliver controlled amounts of medication (1, 2). They can be used to infuse local anaesthetic solutions directly into operative sites for pain management following surgical procedures. The device consists of a reservoir containing the local anaesthetic solution which is delivered by gravity or by electric pump through a catheter implanted directly into the surgical wound. Bupivacaine is an anaesthetic commonly used with postoperative pain pumps (3). A combination of bupivacaine and epinephrine is also used, with the epinephrine inducing vasoconstriction and slowing down the absorption of bupivacaine.

As of July 2008, Health Canada has received 8 incident reports of articular chondrolysis following shoulder surgery that were suspected of being associated with the use of postoperative pain pumps. The pain pumps were used for about 48 hours after surgery. All of the patients received bupivacaine with epinephrine. Chondrolysis was diagnosed between one month and one year after surgery and use of the pain pumps.

Chondrolysis is a progressive degeneration of the cartilage for which the cause is not fully understood (4, 5). Chondrolysis of the shoulder results in narrowing of the joint space, leading to pain and loss of motion; it is a debilitating condition that requires medical attention and possibly surgery (3, 4). Chondrolysis is listed among the possible adverse incidents in the device labelling of pain pumps (1, 2). The device labelling states that the

continuous intra-articular infusion of anaesthetics, particularly when epinephrine is also used, is not recommended.

The association between postoperative pain pumps and the development of chondrolysis is difficult to identify. Indeed, chondrolysis may appear many months after the use of a pain pump (3–5). In addition, confounders such as the concomitant use of health products (e.g., gentian violet, chlorhexidine, bone cement) and radiofrequency devices may be responsible for causing chondrolysis after shoulder surgery (5–10).

Health care professionals are encouraged to follow the instructions for use and refrain from using postoperative pain pumps for continuous intra-articular infusion of local anaesthetics, particularly with epinephrine, after shoulder surgery (1, 2).

Extracted from the Canadian Adverse Reactions Newsletter, Volume 19, Number 1 (2009).

References

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Atomoxetine: serious liver injury

United States of America — The Food and Drug Administration (FDA) continues to receive reports of serious liver injury in patients given atomoxetine. Atomoxetine received FDA approval on 26 November 2002 as the first non-stimulant medication used for the treatment of attention deficit hyperactivity disorder (ADHD) in children (aged 6 years and above) and adults (1).

Atomoxetine's therapeutic action is believed to be due to its selective inhibition of norepinephrine reuptake. From the year 2002 to 2007, approximately 3.3 million patients received a prescription for atomoxetine in the United States. Of those, approximately 2.1 million patients (64%) were children aged 17 years and younger (2).

While a signal for serious liver injury was not detected during premarket clinical trials of atomoxetine, two published post-marketing reports did identify instances of atomoxetine-induced hepatitis (3, 4). In one of these reports, there was a positive rechallenge with atomoxetine. Subse-

quent to these reports, a bolded warning was added in 2004 to the atomoxetine label indicating an increased risk for severe liver injury.

Since the 2004 labelling change, FDA has received six additional reports of serious liver injury in patients taking atomoxetine. Following an evaluation of the information from the drug sponsor and additional literature articles submitted to FDA, the atomoxetine product label was again revised in 2007. The warnings and precautions section of the drug label advises prescribers about the risk for severe liver injury with this drug (1).

Post-marketing reports indicate that atomoxetine is associated with serious idiosyncratic liver injury. Some of the cases reported additional confounding factors, such as occasional acetaminophen use. Some of the cases lacked sufficient clinical detail to convincingly detail the relationship between the use of atomoxetine and liver injury. The mechanism of atomoxetine-induced liver injury remains unknown.

FDA encourages physicians to:

- Inform patients to immediately contact their physician at the first sign or symptom of fatigue, loss of appetite, nausea, vomiting, pruritus, dark urine, jaundice of the sclerae or skin, right upper quadrant tenderness, or unexplained “flu-like” symptoms.
- Determine liver enzyme levels when a patient presents with signs or symptoms of liver injury.
- Discontinue and not resume atomoxetine treatment if patients present with jaundice or laboratory evidence of liver injury

References

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Drotrecogin alfa: ongoing safety review

United States of America — The Food and Drug Administration (FDA) is aware of a retrospective study (1) which has reported an increased risk of serious bleeding events and death in patients with sepsis (a severe illness related to a bloodstream infection) and baseline bleeding risk factors who received drotrecogin alfa. Drotrecogin alfa (*activated*) (Xigris®) is a recombinant human activated protein C indicated for the reduction of mortality in adult patients with severe sepsis who have a high risk of death (2). The baseline bleeding risk factors as defined by this study are the same as those described in the drotrecogin alfa prescribing information.

An editorial (3) accompanying the article stated that one approach to increasing the safety of drotrecogin alfa would be to not administer it to any patients with sepsis and baseline bleeding risk factors, effectively changing a warning in the product labelling to a contraindication. Under FDA regulations, contraindications in the prescribing information describe situations where the risks are known (that is, are not theoretical) and where the risks of use clearly outweigh any possible benefit.

The study was a retrospective medical record review of 73 patients who received drotrecogin alfa. Serious bleeding events

occurred in 7 of 20 patients (35%) who had a bleeding risk factor vs only 2 of 53 (3.8%) patients without any bleeding risk factors. More patients with baseline bleeding risk factors died (13/20; 65%) compared to patients without any bleeding risk factors (13/53; 24.5%). The authors acknowledge that there are limitations to this study, such as its retrospective design and the small size of the patient population, that limit the ability to draw definitive conclusions from the data.

References

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Clopidogrel bisulfate: ongoing safety review

United States of America — The Food and Drug Administration (FDA) is aware of published reports that clopidogrel (Plavix®) is less effective in some patients than it is in others. Differences in effectiveness may be due to genetic differences in the way the body metabolizes clopidogrel (1, 2) or that using certain other drugs with clopidogrel can interfere with how the body metabolizes clopidogrel (3).

Clopidogrel is an antiplatelet drug that is used to prevent blood clots that could lead to heart attacks or strokes in patients at risk for these problems. The drug clopidogrel is a “pro-drug” which means that it has to be metabolized by the body before it can be biologically active and have the effect of preventing blood clots. Understanding that there are differences in how the body metabolizes clopidogrel and there are effects that other drugs may have on its metabolism is important because decreases in the effectiveness of clopidogrel might be avoided, in part, by using other drugs with clopidogrel that do not interfere with its metabolism.

One class of drugs commonly used with clopidogrel is proton pump inhibitors (PPIs). Some reports suggest that use of certain PPIs may make clopidogrel less effective (3, 4) by inhibiting the enzyme that converts clopidogrel to the active form of the drug. Other reports do not suggest this effect (5, 6). Proton pump inhibitors decrease stomach acid and are used to treat frequent heartburn and stomach ulcers. Clopidogrel can irritate the stomach so PPIs are commonly used with clopidogrel to help reduce this irritation. Currently, there is no evidence that other drugs that reduce stomach acid, such as H2 blockers or antacids interfere with the antiplatelet activity of clopidogrel.

References

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Modafinil: adverse skin and psychiatric reactions

Australia — Modafinil (Modavigil®) is a wakefulness promoting agent available since July 2002 for the treatment of patients with excessive daytime sleepiness associated with narcolepsy or chronic shift work sleep disorder and as adjunctive treatment in obstructive sleep apnoea/hypopnoea syndrome. Up to September 2008, 4168 prescriptions had been issued for this medicine.

Recently, international attention has been drawn to the risk of serious adverse skin and psychiatric reactions with modafinil (1, 2). Since 2003, in Australia, 10 reports have been received: two describe skin reactions, five serious psychiatric reactions and three gastrointestinal disturbance, rhinorrhoea and chest pain, respectively.

Nonspecific skin rash may be the earliest presentation of Stevens Johnson syndrome, erythema multiforme or toxic epidermal necrolysis, all of which have

been reported with modafinil overseas (1, 2). Serious, potentially life-threatening skin reactions to modafinil usually present within the first five weeks of treatment but isolated cases have occurred after three months (2).

Although modafinil-associated psychiatric reactions most commonly occur in those with a history of psychosis, depression or mania, they have also been reported in patients without a psychiatric history. Overseas reports of psychiatric reactions have also described hallucinations, aggression and mania.

Prescribers should be cautious when prescribing modafinil to patients with a history of psychosis, depression or mania. Alcohol, drug or illicit substance abuse are also reported risk factors (2). At the first sign of rash, or if patients experience psychiatric symptoms, modafinil should be discontinued and not restarted.

Extracted from Australian Adverse Drug Reactions Bulletin. Volume 27, Number 6 (2008).

References

1. Medicines Healthcare Regulatory Agency (MHRA). *Drug Safety Update*, 2008; vol. 1/8.
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Levothyroxine update

New Zealand — Four brands of levothyroxine have Ministerial consent for distribution in New Zealand. These brands are Eltroxin®, Synthroid®, Goldshield Levothyroxine®, and Eutroxsig®.

Prescribers are reminded that the different brands of levothyroxine are not interchangeable. This means that a change in brand will require thyroid function monitoring, and in some cases

dose adjustment. Prescribers are also reminded to specify the brand of levothyroxine on each prescription to ensure the correct brand is dispensed for each patient.

The Centre for Adverse Reactions Monitoring (CARM) continues to receive adverse reaction reports for all brands of levothyroxine available in New Zealand, although the number of reports has tailed off in recent months. As at 31 December 2008, CARM had received 1384 reports for Eltroxin®, nine reports for Synthroid®, and five reports for Goldshield Levothyrox-ine®. Adverse drug reactions to Eltroxin® have not been reported to the same extent in other countries where the new formulation is used.

Reference: Centre for Adverse Reactions Monitoring. *Prescriber Update*, Volume 30, Number 1 (2009). http://www.medsafe.govt.nz/profs/PUArticles/PDF/Prescriber_Update_Feb09.pdf and www.medsafe.org.nz/hot/alerts/

Temsirolimus: hypersensitivity

United Kingdom/European Union — Hypersensitivity/infusion reactions (including some life-threatening and rare fatal reactions) have been associated with the administration of temsirolimus (Torisel®). These include but are not limited to flushing, chest pain, dyspnoea, hypotension, apnoea, loss of consciousness, and anaphylaxis. The majority of these hypersensitivity/infusion reactions occurred with the first infusion, often within the first few minutes of the start of the infusion, although reactions with subsequent infusions have been reported.

Advice for healthcare professionals:

- Carefully refer to the Summary of Product Characteristics (SPC) instructions for premedication, dilution and administration of the product.

- Patients should be given intravenous diphenhydramine 25 – 50 mg (or similar antihistamine) approximately 30 minutes before the start of each dose of temsirolimus.
- Patients should be closely monitored early during the infusion.
- Appropriate supportive care should be readily available.
- Temsirolimus infusion should be interrupted in all patients with severe infusion reactions, and appropriate medical care administered.
- A benefit-risk assessment should be made prior to continuation of temsirolimus therapy in patients with severe or life-threatening reactions.

Reference: Direct Healthcare Professional Communication dated January 2009 from Wyeth Pharmaceuticals, UK at <http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/>

Aliskiren: new contraindication and warning

European Union — The European Medicines Agency (EMA) has recommended adding a contraindication to the product information for aliskiren, stating that it must not be used in patients who have experienced angioedema when taking aliskiren in the past. The Agency also recommended the inclusion of a warning, stating that patients who develop signs of angioedema should stop treatment and seek medical attention.

Aliskiren, a renin inhibitor, is authorized for the treatment of essential hypertension. It has been authorized in the European Union since August 2007 as Rasilez®, Enviage®, Sprimeo®, Tekturna® and Riprazo®. The EMA's Committee for Medicinal Products for Human Use (CHMP) is recommending

that any patients who develop signs of angioedema should stop aliskiren treatment promptly and seek medical attention.

Reference: *EMA Press Release*. European Medicines Agency recommends new contraindication and warning for Rasilez® and other aliskiren medicines. Doc. Ref. EMA/CHMP/89523/2009. 19 February 2009 at <http://www.emea.europa.eu/>

Continued vaccination with Gardasil®

European Union — The European Medicines Agency (EMA) has reviewed the available information on the two cases of status epilepticus with myoclonus (repeated and prolonged seizures and loss of consciousness) reported in two girls vaccinated with the cervical cancer vaccine Gardasil® in Spain.

Based on the current data, the Agency's Committee for Medicinal Products for Human Use (CHMP) has concluded that the cases are unlikely to be related to vaccination with Gardasil® and that the benefits of Gardasil® continue to outweigh its risks. Therefore the Committee is recommending that vaccination with Gardasil® should continue in accordance with national vaccination programmes in Member States.

Both girls were vaccinated with the same batch of Gardasil, became ill shortly after vaccination, and are now improving. Following the two cases, the Spanish public health authorities stopped vaccination with the batch of Gardasil concerned as a precautionary measure on 9 February 2009. The Italian authorities also stopped vaccination with this batch shortly thereafter. The distribution of the entire batch was stopped on 10 February 2009.

The CHMP and its Pharmacovigilance Working Party are investigating this situation further. The marketing authoriza-

tion holder has been requested to provide a full analysis of the batch, as well as further information on the vaccine's side effects, any similar cases, and possible ways in which Gardasil® could be linked to the cases seen in Spain.

Notes

1. The batch concerned has also been distributed in France, Germany, Italy and the Netherlands. However, it has not been used to date in Germany or in the Netherlands.
2. The approved indication in the EU for Gardasil® is: "... a vaccine for the prevention of premalignant genital lesions (cervical, vulvar and vaginal), cervical cancer and external genital warts (condyloma acuminata) causally related to Human Papillomavirus (HPV) types 6, 11, 16 and 18.
3. The same vaccine is also marketed in the EU as Silgard®.

Reference: *EMA Press Release*. European Medicines Agency recommends continued vaccination with Gardasil®. Doc. Ref. EMA/CHMP/103339/2009. 19 February 2009, at <http://www.emea.europa.eu/>

Erlotinib: use in hepatic impairment and advanced solid tumours

Canada — Erlotinib (Tarceva®) is a human epidermal growth factor receptor type 1/epidermal growth factor receptor (HER1/EGFR) tyrosine kinase inhibitor. It is authorized as monotherapy for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen, and whose EGFR expression status is positive or unknown.

Based on the review of a pharmacokinetic study in patients with advanced solid tumours comparing patients with moderate hepatic impairment and those with normal hepatic function 10 of the 15

patients with moderate hepatic impairment died during treatment or within 30 days of the last dose of erlotinib. Five of the 10 subjects died within one month of initiating erlotinib daily continuous treatment.

Reduced erlotinib doses should be considered for subjects with moderate hepatic impairment. Hepatic function should be closely monitored in patients with pre-existing liver disease or concomitant hepatotoxic medications. Erlotinib dosing should be interrupted if significant changes in liver function tests are observed.

Reference: Communication from Hoffmann-La Roche Limited dated 12 December 2008 at Health Canada <http://www.hc-sc.gc.ca>

Generic piperacillin and tazobactam: medication errors

United Kingdom — Generic versions of piperacillin/tazobactam are now available. These medicines have a different formulation and different compatibilities compared to the brand leader product (Tazocin®) which was reformulated last year. These differences raise the potential for serious medication errors.

Health professionals are requested to take note of the following important information about generic medicines that contain piperacillin and tazobactam:

- Generic piperacillin/tazobactam products must not be mixed or co-administered with any aminoglycoside.
- Generic piperacillin/tazobactam must not be reconstituted or diluted with lactated Ringer's (Hartmann's) solution.
- Piperacillin/tazobactam is licensed for the treatment of a wide range of infections. These medicines are now avail-

able as generic products in addition to the brand leader.

Advice for healthcare professionals:

- Pharmacists should clearly label reconstituted generic piperacillin/tazobactam with a statement that the product must not be mixed or co-administered with aminoglycosides.
- Prescription charts should be checked to ensure that where patients are prescribed both aminoglycosides and generic piperacillin/tazobactam these are not administered at the same time as this can lead to substantial inactivation of the aminoglycoside. Clinical and nursing staff should be advised of the risks with these products.

Reference: Medicines and Healthcare products Regulatory Agency (MHRA) at <http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/>

Safety of artemisinin combination therapy for pregnant women

A trial conducted in northwest Thailand has found that it is safe to use artemisinin combination therapy (ACT) to treat pregnant women with malaria, but that efficacy is inferior to single-drug artesunate treatment. The study, published in *PLoS Medicine*, suggests that the ACT evaluated in the trial, artemether-lumefantrine (AL), may have lower efficacy because drug concentrations were seen to be reduced during pregnancy. The authors suggest that longer, or more frequent, regimens of the drug combination should be evaluated for treatment of pregnant women.

ACT — the combination of two antimalarial drugs to reduce the chance of malaria becoming resistant to either — is now the primary form of treatment for *Plasmodium*

falciparum malaria, which kills nearly one million people per year. ACT may soon be the only effective treatment for malaria, given that the disease has become resistant to many of the older antimalarial drugs, and it has shown to be safe and effective in non-pregnant women. For pragmatic reasons the World Health Organization (WHO) also recommends that ACT is used to treat malaria in mid-late pregnancy, despite the fact that little is known about how well it works in pregnant women.

This trial was conducted on the Thai-Burmese border, an area where malaria transmission is low but highly drug-resistant, meaning that pregnant women who contract the disease are at risk of developing severe malaria that can be fatal to both the mother and her unborn child.

The study sought to compare the safety and efficacy of the most widely used ACT, artemether-lumefantrine (AL), with artesunate, a single artemisinin-derived drug. The 253 women enrolled in the trial had uncomplicated malaria — the stage before the patient needs treatment with intravenous drugs — and were in the second and third trimesters of pregnancy.

Using the PCR adjusted cure rate to assess how each type of treatment cured new infections, it was found that artesunate outperformed AL (89.7% compared to 81.2%), although neither course of

treatment achieved the 95% cure rate recommended by WHO. Few side effects were found with either type of treatment, and the health and development of infants at birth and at one-year of age were similar irrespective of the type of treatment their mothers received.

This is the first trial that examined the use of ACT to treat pregnant women and the finding that it is safe and well-tolerated in the second and third trimesters of pregnancy is significant and welcome. Despite the fact that ACT did not perform as well as in studies of non-pregnant women with uncomplicated malaria, the researchers are careful to warn that this does not mean it cannot be used to treat pregnant women effectively in other endemic regions. Low drug blood levels were observed in the women seven days after treatment, which may explain the reduced efficacy of ACT in this area of Thailand with highly drug-resistant parasites. The researchers conclude by suggesting a higher-dose ACT regimen should now be evaluated for the treatment of pregnant women with uncomplicated malaria.

Reference: McGready R, Tan SO, Ashley EA, et al. A randomised controlled trial of artemether-lumefantrine versus artesunate for uncomplicated *Plasmodium falciparum* treatment in pregnancy. *PLoS Med*5(12): (2008)e253.doi:10.1371/journal.pmed.0050253?request=get-document&doi=10.1371/journal.pmed.0050253 at <http://www.plos.org/press/plme-05-12-mcgregary.pdf>

Spontaneous monitoring systems are useful in detecting signals of relatively rare, serious and unexpected adverse drug reactions. A signal is defined as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually, more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information". All signals must be validated before any regulatory decision can be made.

Regulatory Action and News

Efalizumab: suspension of marketing authorization

European Union — The European Medicines Agency (EMA) has recommended suspension of the marketing authorization for efalizumab (Raptiva®). The EMA's Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of efalizumab no longer outweigh its risks because of safety concerns, including the occurrence of progressive multifocal leukoencephalopathy (PML) in patients taking the medicine.

Efalizumab has been authorized in the European Union (EU) since September 2004 to treat adult patients with moderate to severe chronic plaque psoriasis who have failed to respond to, or who have a contraindication to, or are intolerant of other systemic therapies including ciclosporin, methotrexate and PUVA (psoralen ultraviolet-A).

The CHMP carried out the review following reports of serious side effects, including three confirmed cases of PML in patients who had taken efalizumab for more than three years. PML is a rare brain infection that usually leads to severe disability or death. Two of the three confirmed cases of PML reported to the CHMP resulted in the patient's death. The CHMP also received an additional report of a suspected case of PML which could not be confirmed.

Following review of all available data on the medicine's safety and effectiveness, the CHMP concluded that:

- Efalizumab's benefits are modest.
- In addition to PML, efalizumab is associated with other serious side effects, including Guillain-Barré and Miller-Fisher syndromes, encephalitis, encephalopathy, meningitis, sepsis and opportunistic infections.
- There is not enough evidence to identify a group of patients in which the benefits of efalizumab outweigh its risks, in particular there is a lack of data on effectiveness and safety in patients who have no other treatment options and who may already have a weakened immune system as result of previous treatments.

The CHMP was therefore of the opinion that the risks of efalizumab outweigh its benefits and that the marketing authorization for this medicine should be suspended in the EU.

Prescribers should not issue any new prescriptions for efalizumab and should review treatment of patients currently receiving the medicine to assess the most appropriate alternatives. They should make sure that patients who have been treated with efalizumab are closely monitored for neurological symptoms and symptoms of infection. Patients who are currently taking efalizumab should not stop treatment abruptly, but should make an appointment with their doctor to discuss the most appropriate replacement treatment.

Reference: *Press Release*, Doc. Ref. EMA/CHMP/20857/2009 dated 19 February 2009. <http://www.emea.europa.eu>

Contusugene ladenovec: withdrawal of marketing application

European Union — The European Medicines Agency (EMA) has been formally notified by Gendux Molecular Limited of its decision to withdraw its application for a centralized marketing authorization for the medicinal product contusugene ladenovec (Advexin®) suspension for injection.

Advexin® was expected to be used for the treatment of Li-Fraumeni cancer in patients over the age of 18 years as monotherapy.

The company stated that the reason for withdrawal of the application for Advexin® was based on the company's marketing strategy.

Reference: *Press Release*, Doc. Ref. EMA/690558/2008 of 19 December 2008 at http://list.emea.europa.eu/mailman/listinfo/press_group

Paliperidone: withdrawal of application for extension of indication

European Union — The European Medicines Agency (EMA) has been formally notified by Janssen-Cilag International N.V. of its decision to withdraw its application for an extension of indication for the centrally authorized medicine paliperidone (Invega®) prolonged-release tablets.

Invega® was expected to be used for the treatment of acute manic episodes associated with bipolar I disorder. It was first authorized in the European Union on 25 June 2007 and is currently indicated for the treatment of schizophrenia.

In its official letter, the company stated that the withdrawal was based on feed-

back from early evaluation indicating that the data provided were not sufficient to support approval for this indication and the company's view that it was not in a position to adequately address this issue.

Reference: *Press Release*, Doc. Ref. EMA/683633/2008 of 17 December 2008 at http://list.emea.europa.eu/mailman/listinfo/press_group

First EMA meeting of Committee for Advanced Therapies

European Union — On 15 and 16 January, the European Medicines Agency (EMA) held its first meeting of the new Committee for Advanced Therapies (CAT). The CAT is a multidisciplinary committee, gathering together some of the best available experts in Europe to assess the quality, safety and efficacy of advanced therapy medicinal products (ATMPs) and to follow scientific developments in the field.

ATMPs are medicinal products for human use based on gene therapy, somatic cell therapy or tissue engineering. They may offer groundbreaking new treatment opportunities for diseases and injuries of the human body. The regulatory framework established by the new legislation on ATMPs is designed to ensure the free movement of these medicines within the European Union (EU), to facilitate their access to the EU market, and to foster competitiveness of European pharmaceutical companies in the field, while guaranteeing the highest level of health protection for patients.

The CAT has a pivotal role in fulfilling the objectives of the legislation. One of its main tasks is to prepare a draft opinion on each ATMP application before the Committee for Medicinal Products for Human Use (CHMP) adopts a final opinion on the granting, variation, suspension or revocation of a marketing authorization for the medicine concerned.

Other responsibilities of the CAT include:

- Evaluation and certification of quality and non-clinical data of ATMPs under development by small and medium-sized enterprises.
- Provision of scientific recommendations on the classification of ATMPs.
- Contribution to the provision of scientific advice, including advice on the conduct of pharmacovigilance and risk-management systems of ATMPs, as well as on measures to monitor the continuing effectiveness of these medicines, in liaison with the Scientific Advice Working Party (SAWP).
- Provision, at the request of the European Commission, of scientific expertise and advice as part of any Community initiative related to the development of innovative medicines and therapies that requires expertise on ATMPs.

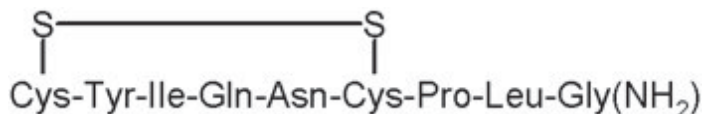
Reference: *Press Release*, Doc. Ref. EMEA/7866/2009 of 16 January 2009 at http://list.emea.europa.eu/mailman/listinfo/press_group

Consultation Document

The International Pharmacopoeia

OXYTOCINUM OXYTOCIN

Draft proposal for the *International Pharmacopoeia* (January 2009). Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax +4122791 4730 or e-mail to rabouhansm@who.int



Relative molecular mass. 1007

Chemical name. L-Cysteinyl-L-tyrosyl-L-isoleucyl-L-glutamyl-L-asparaginyl-L-cysteinyl-L-prolyl-L-leucylglycinamide cyclic (1→6)-disulfide; CAS Reg. No. 50-56-6.

Other name. Alpha-hypophamine.

Description. White or almost white powder.

Solubility. Very soluble in water. It dissolves in dilute solutions of acetic acid and of ethanol.

Category. Uterine-stimulating (Oxytotic).

Storage. Oxytocin should be kept in an airtight container, protected from light, at a temperature of 2 °C to 8 °C. If the substance is sterile, it should be kept in a sterile, airtight, tamper-evident container.

Labelling. The designation on the container should state the oxytocin peptide content (C₄₃H₆₆N₁₂O₁₂S₂) and, where appropriate, that the substance is suitable for parenteral use

Additional information. Oxytocin is hygroscopic.

REQUIREMENTS

Definition. Oxytocin is a synthetic cyclic nonapeptide having the structure of the hormone produced by the posterior lobe of the pituitary gland that stimulates contraction of the uterus and milk ejection in receptive mammals. It is available in the freeze-dried form as an acetate.

Oxytocin contains not less than 93.0% and not more than 102.0% of the peptide $C_{43}H_{66}N_{12}O_{12}S_2$, calculated with reference to the anhydrous and acetic acid-free substance.

By convention, for the purpose of labelling oxytocin preparations, 1 mg of oxytocin peptide ($C_{43}H_{66}N_{12}O_{12}S_2$) is equivalent to 600 IU of biological activity.

Manufacture. The method of manufacture is validated to ensure that, if tested, the substance would comply with the following test:

Amino acids. Examine by means of a suitable amino-acid analyzer that has been appropriately calibrated. Standardize the apparatus with a mixture containing equimolar amounts of ammonia, glycine and the L-form of the following amino acids: lysine, threonine, alanine, leucine, histidine, serine, valine, tyrosine, arginine, glutamic acid, methionine, phenylalanine, aspartic acid, proline, isoleucine together with half the equimolar amount of L-cystine. For the validation of the method, use an appropriate internal standard, such as DL-norleucine.

Test solution Place 1.0 mg of the substance to be examined in a rigorously cleaned hard-glass tube 100 mm long and 6 mm in internal diameter. Add a suitable amount of a 50 per cent V/V solution of hydrochloric acid R. Immerse the tube in a freezing mixture at $-5\text{ }^{\circ}\text{C}$, reduce the pressure to below 133 Pa and seal. Heat at $110\text{ }^{\circ}\text{C}$ to $115\text{ }^{\circ}\text{C}$ for 16 hours.

Cool, open the tube, transfer the contents to a 10 ml flask with the aid of five quantities, each of 0.2 ml, of water R and evaporate to dryness over potassium hydroxide R under reduced pressure. Take up the residue in water R and evaporate to dryness over potassium hydroxide R under reduced pressure; repeat these operations once. Take up the residue in a buffer solution suitable for the amino-acid analyser used and dilute to a suitable volume with the same buffer solution. Apply a suitable volume to the amino-acid analyser.

Express the content of each amino acid in moles. Calculate the relative proportions of the amino acids, taking one-sixth of the sum of the number of moles of aspartic acid, glutamic acid, proline, glycine, isoleucine and leucine as equal to one. The values fall within the following limits: aspartic acid 0.95 to 1.05; glutamic acid 0.95 to 1.05; proline 0.95 to 1.05; glycine 0.95 to 1.05; leucine 0.90 to 1.10; isoleucine 0.90 to 1.10; tyrosine 0.7 to 1.05; half-cystine 1.4 to 2.1; not more than traces of other amino acids are present.

Identity tests

Either test A, or any two of tests B, C and D may be applied.

A. Carry out the examination as described under 1.7 Spectrophotometry in the infrared region. The infrared absorption spectrum is concordant with the spectrum obtained from oxytocin RS or with the *reference spectrum* of oxytocin.

B. Carry out test B.1 or, where UV detection is not available, test B.2.

B.1 Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R6 as the coating substance and a mixture of 70 volumes of dichloromethane R, 30 volumes of methanol R, 6 volumes of water R and 1 volume of glacial acetic acid R as the mobile phase. Apply separately to the plate 10 µl of each of 2 solutions in methanol R containing (A) 5 mg of the test substance per ml and (B) 5 mg of oxytocin RS per ml. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in a current of cool air. Examine the chromatogram in ultraviolet light (254 nm).

The principal spot obtained with solution A corresponds in position, appearance, and intensity with that obtained with solution B.

B.2 Carry out the test as described under test B.1 but using silica gel R5 as the coating substance. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in a current of cool air. Spray with ninhydrin/2-propanol (5g/l) TS. Heat the plate for a few minutes at 120 °C. Examine the chromatogram in daylight. The principal spot obtained with solution A corresponds in position, appearance, and intensity with that obtained with solution B.

[Note from the Secretariat: The following entries will be included under Reagents: “**Ninhydrin/ 2-propanol (5g/l) TS Procedure.** Prepare a 5g/l solution of ninhydrin R in 2-propanol R”. “**Ninhydrin R** See under Triketohydrindene hydrate R”.]

C. Examine the chromatograms obtained in the Assay. The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with the reference solution.

D. The absorption spectrum (1.6) of a 0.30 mg/ml solution, when observed between 240 nm and 330 nm, exhibits a maximum at about 275 nm; the specific absorbance ($A_{1\text{cm}}^{1\%}$) is 14 to 16, calculated with reference to the anhydrous and acetic acid-free substance.

Specific optical rotation. (1.4) Use a 5.0 mg/ml solution and calculate with reference to the anhydrous and acetic acid-free substance; $[\alpha]_D^{20^\circ} = -24.0^\circ$ to -28.0° .

pH value. (2.3) pH of a 20 mg/ml solution in carbon-dioxide-free water R, 3.0-6.0.

Water. Determine as described under 2.8 Determination of water by the Karl Fischer method, Method A, using about 0.10 g of the substance; the water content is not more than 50 mg/g.

Acetic acid content. Determine by 1.14.4 High performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with octadecylsilyl silica gel for chromatography R (5 µm).

Use the following conditions for gradient elution:

Mobile phase A: Dilute 0.7 ml of phosphoric acid (~1440 g/l) TS with 900 ml purified water; adjust the pH to 3.0 with sodium hydroxide (~200 g/l) TS and dilute to 1000 ml with purified water.

Mobile phase B: Methanol R

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0 – 5	95	5	Isocratic
5 – 10	95 to 50	5 to 50	Linear gradient
10 – 20	50	50	Isocratic
20 – 22	50 to 95	50 to 5	Linear gradient
22 – 30	95	5	Isocratic re-equilibration

Prepare the following solutions:

For solution (1), dissolve 15.0 mg of the substance to be examined in a mixture of 5 volumes of mobile phase B and 95 volumes of mobile phase A and dilute to 10.0 ml with the same mixture of mobile phases.

For solution (2), prepare a 0.10 g/l solution of glacial acetic acid R in a mixture of 5 volumes of mobile phase B and 95 volumes of mobile phase A.

Operate with a flow rate of 1.2 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 210 nm.

Inject alternatively 10 µl each of solutions (1) and (2). In the chromatograms obtained, the peak corresponding to acetic acid has a retention time of 3-4 min. The baseline presents a steep rise after the start of the linear gradient, which corresponds to the elution of oxytocin from the column. Calculate the acetic acid content; not less than 60 mg/g and not more than 100 mg/g.

Related substances. Determine by High performance liquid chromatography as described under Assay with the following modifications.

Prepare the following solutions using mobile phase A as diluent. For solution (1) use 0.50 mg of the test substance per ml. For solution (2) dilute a suitable volume of solution (1) to obtain a concentration equivalent to 5.0 µg of oxytocin per ml. Prepare solution (3) using 3 ml of solution (1) and 2 ml of sulfuric acid (~10 g/l) TS, heat carefully in a boiling water-bath for 20 minutes.

Inject 50 µl of solution (3). The test is not valid unless the resolution between the peak due to oxytocin (retention time about 25 minutes) and the peak with a relative retention of about 0.9 is at least 1.4.

Inject alternatively 50 µl each of solutions (1) and (2).

In the chromatogram obtained with solution (1), the area of any peak, other than the

principal peak, is not greater than 1.5 times the area of the principal peak obtained with solution (2) (1.5%). The sum of the areas of all peaks, other than the principal peak, is not greater than 5.0 times the area of the principal peak obtained with solution (2) (5%). Disregard any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

Assay

Carry out the test as described under 1.14.4 High performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with particles of silica gel the surface of which has been modified with chemically bonded octadecylsilyl groups (5 μ m). (Europer 100–5 is suitable.)

Use the following conditions for gradient elution:

Mobile phase A: 15 volumes of acetonitrile R, 15 volumes of phosphate buffer and 70 volumes of water R. (Europer 100–5 is suitable.)

Mobile phase B: 70 volumes of acetonitrile R, 15 volumes of phosphate buffer and 15 volumes of water R.

Prepare the phosphate buffer by dissolving 31.2 g of sodium dihydrogen phosphate dihydrate R in 1000 ml of water R.

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0 – 5	100	0	Isocratic
5 – 20	100 to 94	0 to 6	Linear gradient
20 – 50	94 to 60	6 to 40	Linear gradient
50 – 51	60 to 100	40 to 0	Linear gradient
51–65	100	0	Isocratic re-equilibration

For solution (1) dissolve a suitable amount of the test substance, accurately weighed, in mobile phase A to obtain a solution containing 0.50 mg per ml. For solution (2) dissolve the contents of a vial of oxytocin RS in mobile phase A to obtain a concentration of 0.50 mg/ml Prepare solution (3) using 3 ml of solution (1) and 2 ml of sulfuric acid (~10 g/l) TS, heat carefully in a boiling water-bath for 20 minutes.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 220 nm.

Maintain the column temperature at 40 °C.

Inject 50 μ l of solution (3). The assay is not valid unless the resolution between the peak due to oxytocin (retention time about 25 minutes) and the peak with a relative retention of about 0.9 is at least 1.4.

Inject alternatively 50 μ l each of solutions (1) and (2).

Calculate the content of oxytocin peptide ($C_{43}H_{66}N_{12}O_{12}S_2$) from the declared content of $C_{43}H_{66}N_{12}O_{12}S_2$ in oxytocin RS.

Additional requirement for Oxytocin for parenteral use

Bacterial endotoxins. Carry out the test as described under 3.4 Test for bacterial endotoxins; contains not more than 300 IU of endotoxin per mg.

Impurities

The following list of known and potential impurities that have been shown to be controlled by the tests of this monograph is given for information [structures and systematic names to be included].

A. Carbimido oxytocin

B. Acetyloxytocin

C. α -dimer

D: β -dimer

OXYTOCINUM INJECTIO OXYTOCIN INJECTION

Draft proposal for the *International Pharmacopoeia* (January 2009).
Please address any comments to Quality Assurance and Safety: Medicines, World Health Organization, 1211 Geneva 27, Switzerland. Fax +4122791 4730 or e-mail to rabouhansm@who.int

Description. A clear, colourless liquid.

Category. Uterine-stimulating (Oxytotic).

Storage. Oxytocin injection should be kept protected from light and, unless otherwise indicated on the label, stored at a temperature between 2°C and 8°C.

Labelling. The designation on the container should state the content in IU per ml and the oxytocin peptide ($C_{43}H_{66}N_{12}O_{12}S_2$) content in mg per ml.

Additional information. Strength in the current WHO Model list of essential medicines: 10 IU per ml in 1-ml ampoule.

Oxytocin injection is normally intended for intravenous or intramuscular administration. While it is expected that stocks of Oxytocin injection will be stored at 2 °C to 8 °C in, for example, a hospital pharmacy, small amounts may be held for short periods (30 days) without refrigeration, for example, on a labour ward trolley or by a midwife. Any supplies so held and not used within this period should be discarded.

[Note from the Secretariat: Comment on this aspect of the revised draft together with any supporting stability data would be much appreciated.]

REQUIREMENTS

Oxytocin injection complies with the monograph for “Parenteral preparations”.

Definition. Oxytocin injection is a sterile solution of Oxytocin in a suitable diluent. Oxytocin injection contains not less than 90.0% and not more than 110.0% of the amount of the peptide $C_{43}H_{66}N_{12}O_{12}S_2$ stated on the label.

Identity tests

Either test A or test B may be applied.

A. Carry out the test as described under 1.14.1 Thin-layer chromatography, using silica gel R5 as the coating substance and a mixture of 70 volumes of dichloromethane R, 30 volumes of methanol R, 6 volumes of purified water and 1 volume of glacial acetic acid R as the mobile phase. Apply separately to the plate 20 μ l of each of the following two solutions. For solution (A) evaporate 10.0 ml of oxytocin injection to dryness at 30 °C under reduced pressure (not exceeding 0.6 kPa or 5 mm of mercury) and dissolve the residue in 1.0 ml of methanol R. Prepare solution (B) in methanol R containing 165.0 μ g/ml of oxytocin RS. After removing the plate from the chromatographic chamber, allow it to dry exhaustively in a current of cool air. Expose the plate to iodine vapour and examine in daylight.

The principal spot obtained with solution A corresponds in position, appearance, and intensity with that obtained with solution B.

B. Examine the chromatograms obtained in the Assay. The principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with the reference solution.

pH value. (2.3) pH of the injection, 2.5–5.0.

Assay. Determine by 1.14.4 High performance liquid chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with particles of silica gel the surface of which has been modified with chemically bonded octadecylsilyl groups (5 μ m). (Europer 100–5 is suitable.)

Use the following conditions for gradient elution:

Mobile phase A: 15 volumes of acetonitrile R, 15 volumes of phosphate buffer and 70 volumes of water R. (Europer 100–5 is suitable.)

Mobile phase B: 70 volumes of acetonitrile R, 15 volumes of phosphate buffer and 15 volumes of water R.

Prepare the phosphate buffer by dissolving 31.2 g of sodium dihydrogen phosphate dihydrate R in 1000 ml of water R.

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0 – 5	100	0	Isocratic
5 – 20	100 to 94	0 to 6	Linear gradient
20 – 50	94 to 60	6 to 40	Linear gradient
50 – 51	60 to 100	40 to 0	Linear gradient
51 – 65	100	0	Isocratic re-equilibration

Use the following solutions.

For solution (1) use the undiluted injection. For solution (2) dissolve the contents of a vial of oxytocin RS in the mobile phase A to obtain a concentration of 16.7 µg/ml. Prepare solution (3) using 3 ml of solution (1) and 2 ml of sulfuric acid (~10 g/l) TS, heat carefully in a boiling water-bath for 20 minutes.

Operate with a flow rate of 1.0 ml per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 220 nm.

Maintain the column temperature at 40 °C.

Inject 50 µl of solution (3). The assay is not valid unless the resolution between the peak due to oxytocin (retention time about 25 minutes) and the peak with a relative retention of about 0.9 is at least 1.4.

Inject alternatively 50 µl each of solutions (1) and (2).

Calculate the content of oxytocin peptide ($C_{43}H_{66}N_{12}O_{12}S_2$) from the declared content of $C_{43}H_{66}N_{12}O_{12}S_2$ in oxytocin RS.

Recent Publications, Information and Events

Low availability, high prices keep essential medicines out of reach

World Health Organization — An alarming lack of availability of essential medicines in the public sector drives patients to pay higher prices in the private sector or go without, according to a WHO study reported *The Lancet*. The results confirm that governments must do more to improve access to essential medicines as part of their efforts to make national health systems more efficient and equitable.

The study analysed data from surveys in 36 countries from all WHO geographical regions and World Bank income groups. Results show an average public-sector availability of only 38% across surveys. This forces patients to buy medicines from the private sector where treatments are more expensive and frequently unaffordable. In Africa, for example, the lowest-paid government worker needs to spend two days' salary each month to purchase diabetes treatment using the lowest-priced generic medicine. When the originator brand is used, costs escalate to over eight days' wages.

On the pricing side, the study revealed that "cuts" taken by wholesalers, distributors and retailers plus government taxes and duties are driving prices beyond affordability in many countries. In some countries, add-on costs can double the public-sector price of medicine, while in the private sector, wholesale mark-ups ranged from 2% to 380%, and retail mark-ups ranged from 10% to 552%.

The results cover 15 medicines included in at least 80% of surveys, as well as four

specific medicines used to treat asthma, diabetes, hypertension and acute infections. The figures are adjusted to account for differences in buying power of local currencies and then compared to international reference prices, allowing for cross-country comparison.

The work is part of an ongoing joint effort between WHO and Health Action International (HAI) to highlight and improve availability and affordability of essential medicines, especially in low- and middle-income countries.

Reference: Cameron A, Ewen M, Ross Degnan, D. et al. Medicines prices, availability and affordability in 36 developing and middle-income countries: a secondary analysis. *Lancet*, 2009. **373**:24–9

Sources and prices of selected medicines for children

Formulations suitable for children (paediatric formulations) are often not available in the market place, for many reasons, including insufficient information on sources and prices. In May 2007 the World Health Assembly endorsed the WHO Resolution on 'Better Medicines for Children' and published the 'Model List of Essential Medicines for Children'. The global campaign 'Make Medicines Child Size', launched at the same time by WHO is raising awareness and accelerating action to improve the availability of and access to safe and child-specific medicines.

UNICEF in collaboration with WHO is pleased to present *Sources and Prices of Selected Medicines for Children*. The publication provides up-to-date information on the availability of products and

sources, as well as indicative prices of medicines in formulations suitable for children.

This publication contributes to the effort to increase access to appropriate medicines by identifying sources and prices for selected products indicated in the treatment of diseases in children. The list of products selected is based on the 'Model List of Essential Medicines for Children' at [http://www.who.int/childmedicines/publications/EMLc%20\(2\).pdf](http://www.who.int/childmedicines/publications/EMLc%20(2).pdf)

Reference: http://www.unicef.org/supply/index_47129.html

Two international summer courses in the Netherlands

The Division of Pharmacoepidemiology and Pharmacotherapy at Utrecht University, the Netherlands, is offering two challenging international summer courses in Pharmacoepidemiology and Drug Safety and Pharmaceutical Policy Analysis (in collaboration with WHO). Both courses will cover key issues in each field and focus on the most important research methods used. All course teachers have extensive expertise in their field. In addition, there is a cultural and social programme arranged to make sure that participants experience the best of Utrecht.

M8 Pharmacoepidemiology and Drug Safety (29 June – 3 July 2009)

With the prospect that innovative drug therapies will be introduced in the coming years, society demands new approaches and concepts for comparative risk/benefit evaluation. These evaluations are carried out once therapies have been used widely in daily practice. Assessment of safety and risk management of different drug therapies is done in the framework of observational epidemiological studies (proof of safety, proof of effectiveness). This is the logical next step after randomized clinical trials, which are designed to provide evidence of efficacy.

The course will cover key issues in pharmacoepidemiologic and drug safety research. Special topics include data bases and molecular pharmacoepidemiology. All course teachers have extended expertise in the design and conduct of pharmacoepidemiologic studies.

The intensive programme covers the following topics:

- Study design and methods.
- Confounding and other biases.
- Methods in drug safety research.
- Drug safety and risk management.
- Overview of pharmacoepidemiological databases.
- Molecular pharmacoepidemiology.
- Drug utilization research.
- Synthesis, case studies and public health.

M7 International Pharmaceutical Policy Analysis (6–10 July 2009)

Medicines are among the most regulated products in society. From the earliest pre-clinical stages onward, policy makers want to foster the development of safe, effective and affordable medicines for patients in need of pharmacotherapy. When a drug reaches the market, it is the beginning of a process of complex interactions between patients, prescribers, insurers, pharmaceutical companies and governments. Furthermore, from a global perspective, the reality is that two billion people do not have access to essential medicines. The inequity in access to medicines is still a defining characteristic of the global pharmaceutical market place.

This course will cover these issues from a scientific, regulatory, public health and

international policy perspective. As a collaborator on this course, WHO will provide faculty for several of the sessions.

An intensive programme covers the following topics:

- New medicines policy — methods for evaluating policy.
- Methods in pharmaceutical policy analysis.
- Pharmacoepidemiology contribution to pharmaceutical policy analysis.
- Drug usage, adherence to therapy and patient needs.
- Regulatory issues and challenges.
- Access, affordability and reimbursement systems.
- Ethics and equity.
- Current challenges in drug innovation.
- Synthesis, case studies and public health.

Reference: www.utrechtsummerschool.nl/

Global Politics of Pharmaceutical Monopoly

This new book explains why the twin challenges of high medicines cost and the absence of appropriate or effective treatments for many of the diseases affecting patients are in fact two sides of the same coin. It analyses the latest mechanisms and policy changes that may help repair the broken system of medical innovation and access to medicines today.

In particular, the book highlights recent alternative mechanisms to encourage medical research and development in a way that also ensures access to the developed product by separating the cost of research and development from the price of diagnostics, medicines, and vaccines.

The objective of the book is to spur efforts towards a patent pool, to speed up access to newer medicines, and boost initiatives that make use of alternative financing mechanisms in order to develop new, more appropriate treatments that respond to medical needs.

An open access version of *The Global Politics of Pharmaceutical Monopoly Power* is freely available on the MSF Access Campaign website: <http://www.msfacecess.org>