

# Manual



**Zaponex Treatment Access System**



## Legal Notices<sup>4</sup>

### Copyrights and trademarks

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**Leyden Delta B.V.** (hereinafter referred to in this manual as 'Leyden Delta') is the Marketing Authorisation Holder (MAH) for Zaponex<sup>®</sup> (clozapine) in the United Kingdom (UK). Leyden Delta's head office address is: Neerboscheweg 620, 6544 LL Nijmegen, the Netherlands.

**Zaponex<sup>®</sup>** (hereinafter referred to in this manual as 'Zaponex'), the **Zaponex Treatment Access System<sup>®</sup>** (**ZTAS<sup>®</sup>**, hereinafter referred to in this manual as 'ZTAS'), and **BloodResults<sup>®</sup>** (hereinafter referred to as 'BloodResults', or the 'BloodResults' system) are registered trademarks.

**ZTAS** refers to both the **monitoring system** and to the support **team**, together they comprise the Zaponex Treatment Access System. The ZTAS fulfils the requirements for the safe treatment of patients with Zaponex, as outlined in section 1 of the Zaponex [Summary of Product Characteristics](#) (SmPC).

**BloodResults** is a web-based application used by Magna Laboratories to report full blood count and clozapine assay results of ZTAS-registered patients; the results reported via the BloodResults application are accessible online for healthcare providers associated with a patient in ZTAS via the weblink [www.bloodresult.co.uk](http://www.bloodresult.co.uk).

The **ZTAS privacy notice** is a document explaining why Leyden Delta BV collects personal information from healthcare providers and patients who are involved with, or who are receiving, Zaponex treatment, and how we use, process and store it. The **ZTAS privacy notice** is a controlled document. A current copy of the ZTAS privacy notice can be accessed from the ZTAS website [www.ztas.co.uk](http://www.ztas.co.uk) or will be sent on request.

For other definitions of ZTAS terminology [Appendix 2 – Abbreviations and terminology](#)

### Disclaimer

The **ZTAS Manual** provides an overview of the Leyden Delta B.V. Zaponex Treatment Access System (**ZTAS<sup>®</sup>**). This document is for **reference only**. A controlled and current copy of the ZTAS manual is available for ZTAS-registered healthcare professionals from the secure ZTAS website.



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## 1 Introduction

### 1.1 ZTAS

The Zaponex Treatment Access System (ZTAS®) is a web-based patient monitoring system used to monitor patients treated with Zaponex® (Clozapine) in the United Kingdom (UK).

Zaponex is the proprietary brand of clozapine marketed by Leyden Delta. To mitigate the risks associated with the use of clozapine, additional risk minimisation activities are applicable to all clozapine brands available in the UK. Access to clozapine is controlled, and it can be prescribed only by physicians, and dispensed only by pharmacists registered with the ZTAS, who are aware of the risks associated with the product, and to patients for whom the benefits of treatment are expected to outweigh the risks. The Zaponex UK Official recommendations are stated in the [Zaponex SmPC](#) (section 1) and are similar for the other clozapine brands.

ZTAS was developed and is maintained by Leyden Delta to comply with the requirements of the Medicines and Healthcare Products Regulatory Agency (MHRA) to ensure that healthcare providers treat their patients with Zaponex safely in accordance with the product information. Several clinical specialists (psychiatrists, pharmacists and haematologists) were consulted during the development of ZTAS. The ZTAS monitoring service is operated by the ZTAS department of Leyden Delta.

#### 1.1.1 Office hours and ZTAS website

ZTAS offers a round-the-clock service. Office hours are from 8.30 am to 5 pm on week days (Monday to Friday). During office hours ZTAS is supported by a medical information service for general enquiries regarding clozapine treatment (see [1.9 Medical Information, advice and haematological queries](#)). Outside office hours an on-call service is available for urgent enquiries.

Contact details for ZTAS, the ZTAS registration forms, the ZTAS privacy notice, the Zaponex Summary of Product Characteristics (SmPC) and Zaponex Patient Information Leaflet (PIL) can be found on the ZTAS website [www.ztas.co.uk](http://www.ztas.co.uk). Relevant contact details for ZTAS and ZTAS partners are also available in [Appendix 1 – Contact information](#).

#### 1.1.2 ZTAS objectives

- To assist healthcare providers maintain the safety of patients who are being treated with Zaponex and to minimise the risk of agranulocytosis/neutropenia. The White Blood Cell (WBC), neutrophil, eosinophil and platelet counts are recorded on a regular basis for each patient.
- To alert healthcare providers to any abnormalities regarding their patients' blood results (ZTAS monitoring is limited to WBC, neutrophil, eosinophil and platelet cell counts).
- To prevent the re-challenge of clozapine (of any brand) for any patient who has (previously) experienced agranulocytosis/neutropenia/leukopenia whilst taking clozapine
- To control the access to, and maintain a closed distribution system for Zaponex
- To provide information and advice on Zaponex and ZTAS to all healthcare providers
- To promote the safe prescribing, dispensing and use of Zaponex

## 1.2 Compliance

Non-compliance with the procedures for safe treatment with Zaponex as outlined in the Zaponex SmPC and in this ZTAS Manual is potentially dangerous for patients. If there are any issues associated with compliance, ZTAS will contact the parties involved in order to discuss the situation.

In certain situations, it may be necessary to deviate from the ZTAS procedures outlined in this ZTAS Manual. However, deviations from the procedures can only be accepted after approval from ZTAS and/or, if applicable, after approval from the Medical Advisor or the Medical Director. There is no waiver for blood testing: Zaponex may only be dispensed if a valid blood result is present for the patient.



### 1.3 Amendments to the ZTAS Manual and ZTAS privacy notice

The ZTAS Manual and ZTAS privacy notice are periodically reviewed and updated and are available to healthcare providers for reference via the ZTAS website. New versions are effective from their issue date. Updates to the **ZTAS Manual** will be made available to all registered healthcare providers via the secure section of the ZTAS website ([www.ztas.co.uk](http://www.ztas.co.uk)). The issue date is displayed at the bottom of each page except for the front page.

A current version of the **ZTAS privacy notice**, which explains why Leyden Delta collects personal information from healthcare providers and patients for the ZTAS, and how we use, process and store this information, can be found on the public section of the ZTAS website.

### 1.4 Adverse event reporting

The ZTAS routinely monitors blood results for abnormalities in White Blood Cells (WBC), neutrophils, eosinophils and platelet counts. Abnormalities in these parameters (i.e. when outside agreed safe ranges) are considered haematological adverse events associated with Zaponex use.

By registering with the ZTAS, healthcare providers involved with the treatment of patients with Zaponex commit to the ZTAS requirements for reporting adverse events. In case of Amber, Red or 'Out of Range' results (see section [5 - Blood Monitoring](#)), or any other information received by ZTAS that indicates an adverse event, the healthcare provider will be requested to complete an adverse event report.

Healthcare providers are encouraged to report any clinically significant abnormalities in a patient's physical or mental status. Adverse events should be reported to ZTAS within three working days from their occurrence by telephone and/or email. Reported adverse events will be escalated to the Leyden Delta Drug Safety Department and follow-up may be requested from the healthcare provider. Leyden Delta will follow up on all adverse events in accordance with the applicable legislation.

Adverse events may also be reported directly to the MHRA Yellow Card Scheme. Reporting forms and information can be found at [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or via the MHRA Yellow Card app.

Adverse event reporting is essential for the ongoing evaluation of the balance of a medicine's benefits and risks and contributes to factual and up-to-date product information.

### 1.5 Zaponex product complaints

Any problems observed in relation to Zaponex tablets or packaging should be reported to ZTAS as a Zaponex drug product complaint. Drug product complaints should always be reported with a clear description of the complaint. The complaint notification should include a description of the type of product concerned and a reference to the batch number. Additionally, any evidence (e.g. picture) substantiating the product complaint should be attached to the complaint notification. If the drug product complaint concerns a problem related to a specific pack or the tablets, any relevant evidence, or details should also be sent to Leyden Delta to substantiate the complaint and/or to facilitate its handling.

Drug product complaints will be escalated to the Leyden Delta Quality Assurance Department, who will investigate the complaint and report relevant conclusions regarding the investigation back to the reporter/healthcare provider.

### 1.6 Queries and complaints related to confidentiality of information in the ZTAS

Leyden Delta collects and processes personal information from patients and healthcare providers for the purpose of the ZTAS. The ZTAS privacy notice (available from [www.ztas.co.uk](http://www.ztas.co.uk)) explains how this data is used, processed and stored in accordance with the applicable Data Protection Legislation<sup>1</sup>.

The safety and security of the ZTAS computerised systems is in accordance with the strict GxP quality standards that are applicable for computerised systems used in support of a regulated process and as demanded by regulatory requirements within pharmaceutical industry

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<sup>1</sup> [See Appendix 2](#)



Individuals whose data is collected and processed by Leyden Delta can expect that we keep their records confidential. If you have a question about our privacy notice, or if you notice that personal information from ZTAS has unintentionally been disclosed to unauthorised individuals, or the integrity of the data has been compromised, please inform the ZTAS team, or contact our Data Protection Officer directly via [dataprotectionofficer@ztas.co.uk](mailto:dataprotectionofficer@ztas.co.uk).

Queries and/or complaints related to the processing of personal information of patients and healthcare providers associated with the ZTAS, including notifications of personal data breaches, will be escalated to Leyden Delta's Data Protection Officer and the Quality Assurance Department and registered in our quality management system. A notification of a personal data breach/complaint will be investigated and relevant conclusions will be reported back to the complainant/reporter. If a personal data breach has occurred, its impact on the data subjects' rights and freedoms will be assessed. A personal data breach that poses a high risk of harm to one or more data subject(s), or causes detriment (which can include emotional distress as well as physical or financial damage) will be reported by Leyden Delta to the UK Data Protection Authority (i.e. Information Commissioners Office).

## 1.7 Parties in ZTAS

The following parties are involved with ZTAS:

- Consultant psychiatrist
- Clozapine pharmacist / pharmacy
- Supporting healthcare professionals registered with ZTAS
- Shared care prescriber (usually a GP, as part of a shared care protocol)
- Haematology laboratory
- Leyden Delta – ZTAS monitoring service
- Alloga UK – Distributor of Zaponex

Note: Consultants and clozapine pharmacists may nominate staff members to assist them in their work for ZTAS. A person nominated by a consultant psychiatrist or clozapine pharmacist is referred to by ZTAS as a proxy.

### 1.7.1 Conditions and responsibilities for collaboration with ZTAS

ZTAS is a controlled access programme for Zaponex. It ensures that access to Zaponex for healthcare providers and patients is controlled via a closed distribution system.

Zaponex treatment requires at least:

The involvement of a consultant psychiatrist (or a specialist in the fields of psychiatry, neurology or elderly care), a ZTAS-registered pharmacy with a nominated clozapine pharmacist; and a laboratory or a ZTAS Point of Care Testing (POCT) system that is qualified to analyse the patients' blood samples.

- A patient can only be treated with Zaponex if the consultant, the clozapine pharmacist and the patient are registered with ZTAS and arrangements have been made to process the patient's ZTAS blood samples.
- Zaponex treatment must be supervised by a specialist in the field of psychiatry (or another relevant specialty in the context of the indications for Zaponex use); this specialist will remain responsible throughout the patient's Zaponex treatment as supervising specialist.
- All prescribing physicians must register with ZTAS.
- Only pharmacies registered with the ZTAS, represented by a clozapine pharmacist who is authorised to supply Zaponex to patients, can order Zaponex from our distributor.

Important aspects of the closed distribution system for Zaponex are referred to as 'responsibilities' in the ZTAS scheme. The patient's consultant has end-responsibility for the treatment and prescribing of Zaponex. The patient's dispensing pharmacy and nominated clozapine pharmacist are responsible for ensuring the safe dispensing of Zaponex to patients.

In order to understand the restrictions applicable for the safe dispensing of Zaponex to patients, the clozapine pharmacist must undergo training before their registration with ZTAS can be completed (see section 2.1 [ZTAS Training](#)).

The conditions for the safe prescribing and dispensing of Zaponex are outlined in the Zaponex SmPC and in this manual and are summarised below:



- Zaponex may only be prescribed by a consultant or physician who is registered with the ZTAS.
- Zaponex may only be dispensed to patients who are registered with the ZTAS.
- There must always be a current, valid blood result for the patient before any Zaponex is dispensed.
- Zaponex may only be dispensed under the responsibility of a ZTAS-registered clozapine pharmacist.

Clozapine pharmacists will be requested to periodically confirm their awareness of these restrictions and to confirm that they are still the nominated clozapine pharmacist for the pharmacy.

To facilitate the treatment of patients with Zaponex, healthcare providers must provide ZTAS with personal information about themselves, and personal and *sensitive personal data* (also referred to as '*special category data*' under applicable Data Protection Legislation<sup>2</sup>) relating to their patients. The ZTAS department of Leyden Delta processes personal and healthcare information received from healthcare providers in accordance with the Data Protection Legislation.

Healthcare providers are considered data controllers in respect of the personal data relating to their patients who are treated with Zaponex and whose data is submitted to ZTAS. As such, they are responsible for complying with Data Protection Legislation, including ensuring that the data they provide is accurate and, where necessary, up to date (see [7 - Maintaining an up-to-date database](#))

By completing and submitting the appropriate registration form, a healthcare provider confirms to ZTAS that the patient (and/or legal guardian if the patient is under 18) has been informed:

- about the procedures that must be followed for monitoring a patient's health when Zaponex is prescribed and dispensed to the patient;
- about ZTAS's processing of their personal information (by referring to the ZTAS privacy notice) and that this processing may include the transfer of personal information to the 'Central Non Re-challenge Database' (CNRD).

When ZTAS receives a completed patient registration form, ZTAS assumes that healthcare providers have informed their patient about the transfer of relevant personal data to ZTAS (see [3.2 Informing the patient](#)).

ZTAS-registered healthcare providers are granted access to their patients' personal and healthcare data via the ZTAS database. Such access is granted based on the principle of legitimacy of access to information, i.e. on a 'need to know basis'. Consultants and clozapine pharmacists can authorise the registration of proxies (see [2.3 Sharing information in a care team](#)).

Healthcare providers are expected to have appropriate technical and organisational measures to ensure that neither unauthorised nor unlawful processing of, or accidental loss, destruction or damage to the personal and healthcare information of their patient(s) occurs. Such measures include but are not limited to:

- ensuring confidentiality of their patients' data by limiting access to the ZTAS and BloodResults database systems to authorised proxies/ members of staff who legitimately require access to help them care and treat patients with Zaponex;
- periodically reviewing the list of authorised proxies and/or members of staff who have access to the group-email address provided to ZTAS (see [2.3.2 Group email](#)) to determine whether their continued access to the information of ZTAS-registered patients is necessary and legitimate (see [7 - Maintaining an up-to-date database](#)); and
- keeping passwords and log-on details for the ZTAS database systems confidential and not sharing them.

As part of the requirement for keeping information up to date, it is mandatory for both the consultant and the pharmacy to provide ZTAS with an email address that is suitable for the receipt of (pseudonymised) communications from ZTAS relating to ZTAS-registered patients.

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<sup>2</sup> See Appendix 2



ZTAS will send Patient Registration Confirmations, Reminders, Warnings and Alerts to both consultants and clozapine pharmacists using the email address(es) they provide. The healthcare providers shall ensure that all communications sent by ZTAS to the email address(es) provided to ZTAS are kept secure and confidential.

## 1.8 Blood sample testing

Patients who are treated with Zaponex must undergo regular blood testing (see [5 Blood Monitoring](#)). An arrangement with an accredited laboratory must be in place for processing ZTAS blood samples. This arrangement must ensure that blood samples are analysed and reported to the patient's physician and to ZTAS within 24 hours from receipt of the sample by the laboratory. For Point of Care Testing (POCT), blood samples are analysed and results reported to ZTAS and to the patient's consultant within 8 hours from sample taking (see [1.8.3](#)).

The relevant test for a ZTAS blood sample is a full blood count with a differential.

To ensure that the blood results are accurate and that they provide a sound basis for clinical decisions, any laboratory or POCT system that is used for the analysis of ZTAS blood samples must be able to demonstrate participation in the National External Quality Assurance Scheme (NEQAS) or an equivalent external quality assurance scheme for haematology (e.g. via UKAS accreditation according to ISO 15189 [i.e. standard for medical laboratories]) that covers the type of blood testing relevant to ZTAS.

### 1.8.1 Local laboratory

A hospital or healthcare trust/board participating in ZTAS must have an arrangement with a local laboratory that can demonstrate a valid, external certification for haematology (e.g. NEQAS or UKAS). The local laboratory's details must be provided to ZTAS. A local laboratory should be used when ZTAS blood samples need to be processed quickly (e.g. urgent samples following a Red result).

With the approval of ZTAS, a local laboratory may also be used for testing routine ZTAS blood samples. If a hospital or trust/board chooses this option, a formal arrangement between the laboratory, the hospital/trust and ZTAS must be in place. The trust/local laboratory is then responsible for forwarding the results of ZTAS blood samples to the ZTAS office according to set timelines. The trust/hospital should also ensure there is a system in place for screening of local results that become available outside the regular ZTAS office hours (see section [1.1.1 – ZTAS office hours](#)). This system must ensure:

- such results are screened for abnormalities on parameters monitored by ZTAS, and that
- if a result contains abnormal values for one of the ZTAS monitored parameters, a notification is urgently sent to the requester of the test and/or on-call pharmacy staff
- the abnormal result is manually entered onto the ZTAS by a local ZTAS-registered user, so that all healthcare providers involved with the patient's care can be aware of the abnormal values and effective treatment and follow-up can be initiated in a timely manner.

### 1.8.2 Central laboratory

ZTAS supports the use of a central laboratory for the analysis of routine blood samples for patients treated with Zaponex. The ZTAS central laboratory service is provided by Magna Laboratories (see [APPENDIX 1 – Contact information](#)).

Trusts/ health boards that have chosen to have routine blood samples analysed at the ZTAS central laboratory will receive starter packs and patient-specific labels from the central laboratory service. The starter packs contain blood-sampling kits, request forms for re-ordering new kits and all other necessary consumables.

Re-ordering new blood-sampling kits is the responsibility of the site. Instructions on how to order blood kits are enclosed in the starter pack. Both the ZTAS website and Magna Laboratories website ([www.magnalabs.co.uk](http://www.magnalabs.co.uk)) link to a dedicated online order form that can be used to re-order laboratory support materials.



In line with Laboratory Quality Assurance procedures, the central laboratory will only process a sample if the sample tube and request form contain sufficient patient identifiers. Before bloodwork is sent to the laboratory, please make sure that both sample tube and form have this information (e.g. patient name, ZTAS PIN, and date of birth). It is advisable to use patient-specific labels to identify a patient on for both the sample tube and the associated request form.

Samples can be sent to the central laboratory in the following ways:

- *Post (Royal Mail service)*: all blood-sampling kits include pre-paid postage and self-addressed envelopes
- *Courier*: when a large number of blood samples need to be transported, Magna Laboratories can arrange a courier collection.

The results of WBC, neutrophil, eosinophil and platelet counts as analysed by the ZTAS central laboratory are automatically transferred to the ZTAS system. However, since a blood result includes additional parameters that may concern clinical information relevant for a patient's treatment, it is our 'duty of care' to make the values of the full results available to the patient's healthcare providers. Complete blood count results are reported to the consultant (see [1.8.5 BloodResults system](#)).

### 1.8.3 Point of Care Testing

ZTAS has a Point of Care blood Testing (POCT) service in place that has been approved by the Medicines and Healthcare Products Regulatory Agency (MHRA). POCT provides a means of testing blood samples outside the laboratory setting. The analysis equipment is operated by trained, non-laboratory staff. POCT makes it possible to test patients' blood and dispense Zaponex on the same day. It is therefore an important factor in improving patient care. Because the blood analysis takes place outside of the laboratory setting, a system must be in place to ensure that the quality of POCT results can be trusted and that they are of comparable quality to the results from a certified laboratory. Strict guidelines on the use of in vitro POCT devices have been issued by UK regulatory authorities<sup>3</sup>. These guidelines form the quality backbone for the implementation and operation of the ZTAS POCT service.

#### ZTAS POCT Service

The ZTAS POCT service works with local POCT systems that are under strict quality control by ZTAS POCT backend application software.

A **ZTAS POCT system** is made up of a Sysmex Poch-100i blood analyser linked to a computer that has dedicated application software installed that communicates with the ZTAS via the internet. Results received from a ZTAS POCT system are validated by the ZTAS POCT backend application software; if they are confirmed as valid results, the WBC, neutrophil and platelet counts are forwarded on and automatically uploaded onto the ZTAS system. Complete blood count results are reported to the consultant via email.

The **ZTAS POCT service**:

- monitors the quality and the operation of local ZTAS POCT systems
- monitors the quality of data submitted by POCT operators and the skills of POCT operators
- maintains records of trained POCT operators, results and QC lot information

The service includes:

- support with the implementation of POCT at new sites
- POCT Operator training
- Remote help desk support
- quarterly supplies and technical maintenance for the POCT analyser.

A ZTAS POCT system can only be implemented if a trust/ health board has a sufficient number of patients who will be using the service and if the appropriate infrastructure is in place to ensure the system can be operated safely.

Elements of this infrastructure are:

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<sup>3</sup> [MHRA, Management and use of IVD point of care test devices](#)



- involvement of an accredited local laboratory to ensure contingency procedures for analysis of blood samples in the event of a POCT system failure and for haematological expertise.
- a multidisciplinary POCT committee that oversees the use of POCT within the trust/ health board
- a POCT coordinator, usually a senior healthcare professional who can assume overall responsibility and authority for the Zaponex POCT service within the trust/health board. The POCT coordinator is responsible for the results and the correct usage of the equipment and has a major role in clinical governance.
- Each trust/health board should nominate one person among the members of their POCT service as Main Point of Contact for ZTAS (MPOC). This person should have day-to-day involvement in the clozapine services and can act as a central point of contact for ZTAS in case of any issues or concerns.

Within the trust/health board, lines of accountability must be established and local policies and procedures for POCT should be in place on, for example:

- training
- POCT working practice
- quality assurance and record-keeping
- participation in and adherence to the NEQAS
- adverse incident reporting

The implementation of a ZTAS POCT system within a trust/ health board will be supported by dedicated ZTAS staff.

#### 1.8.4 Clozapine plasma assays

Magna Laboratories, the ZTAS central laboratory, also offers ZTAS healthcare providers a service for measuring clozapine plasma levels. Request forms for this service are included in the starter packs. Sites not using the central laboratory service for routine blood testing should contact the laboratory directly to request plasma assay request forms [APPENDIX 1 – Contact information](#). Magna Laboratories reports clozapine plasma assay results directly to the requesting healthcare provider in a format of their choice and via the BloodResults system (see 1.8.5).

#### 1.8.5 BloodResults system

The ZTAS central laboratory, Magna Laboratories, reports the results of all full blood count (FBC) and assay test results for ZTAS-registered patients via the BloodResults web-application at <http://www.bloodresult.co.uk>.

The BloodResults application has been developed by Leyden Delta and Magna Laboratories to provide ZTAS-registered healthcare providers with a flexible method for receiving FBC and clozapine assay results analysed by Magna Laboratories. The BloodResults reporting platform enables clinicians (e.g. consultants and shared care prescribers) to view their patient's clinical results online. By email notifications are sent to the clinician to let them know that new results are available for online review. Consultants, shared care prescribers and clozapine pharmacists associated with patients in the ZTAS automatically receive information to access the BloodResults system so that they can review their patients' FBC and clozapine assay results online. To aid clinical assessment, clozapine assay results can be viewed in the context of historical results in the system. The BloodResults system provides graphs that display relevant parameters of the assay results and result trends.

Consultants and clozapine pharmacists may grant trusted members of their care team access to their patients' results data in BloodResults via a 'ViewAccount'. The ViewAccount provides a consultant or clozapine pharmacist with an easy way to share relevant clinical data with care team members while at the same time allowing them to remain in control of the access to their patients' data. To help healthcare providers to keep the data on the BloodResults system confidential, the ViewAccount password automatically expires every 3 months, after which the owner of the ViewAccount will need to re-distribute access details to members of the care team. The healthcare provider must only provide access to the ViewAccount to those members of the team who require access in order to provide treatment to patients.



The online BloodResults systems provides access to new and historical FBC and assay results and the access to result information can be shared with trusted members of the care team to provide optimum flexibility for organising continuity of care for patients, whilst confidentiality of patient data remains safeguarded.

### **1.9 Medical Information, advice and haematological queries**

Medical advice concerning the treatment of patients with Zaponex is available through ZTAS 24 hours a day, 7 days a week. During office hours the Medical Information Service is available by phone, and email. An out-of-hours, on-call service is available for urgent advice that cannot wait until the next working day. Questions regarding all aspects of patient care can be posed, including side-effect management, blood monitoring procedures, drug interactions and the medical management of patients who develop neutropenia. The Medical Information Service is staffed by a team of Medical Information Officers and Medical Advisors. If warranted, medical and/or haematological advice is substantiated by an experienced consultant haematologist at the Radboud University Nijmegen Medical Centre (the Netherlands).

It should be noted that the ZTAS medical advisors and Medical Information Officers can never assess the full clinical situation of a patient; therefore, the medical advice provided should not be regarded as a substitute for a consultation with a local haematologist/specialist. Medical decision-making remains the responsibility of the treating healthcare provider. ZTAS-registered physicians and pharmacists are advised to have access to a local haematologist or general internist/physician for patient-specific treatment advice on haematological matters.

The secure section of the ZTAS website provides a wide range of medical information, including fact sheets on the management of side-effects of clozapine, guidelines, and a frequently asked question list. These materials are continuously supplemented and updated.

### **1.10 Shared Care**

ZTAS facilitates the treatment of patients with Zaponex in a shared care environment. This means that, although the patient's Zaponex treatment remains under the supervision of a specialist in psychiatry (or in other relevant area), the daily management of the patient may be delegated to another physician, e.g a GP. The shared care prescriber may arrange for blood sampling and may write routine prescriptions for the patient. All changes in prescribing remain the responsibility of the consultant.

To further support the treatment of a patient with Zaponex in a local care environment, the patient may collect their prescription from a community pharmacy, on the condition that both the shared care prescriber and the community pharmacist are registered with ZTAS (see [4 – Shared Care Registration](#)).



## 2 Registration with ZTAS

### *To register with ZTAS*

- A healthcare provider must be able to work adequately with ZTAS (see section 2.1)
- A completed healthcare provider registration form must be submitted to ZTAS

### 2.1 ZTAS training

The objective of ZTAS training is to ensure that healthcare providers involved in the treatment of patients with Zaponex are aware of the restrictions for prescribing and dispensing of Zaponex to patients, as outlined in the Zaponex SmPC and in this manual. Additionally, healthcare providers will be trained to work with the ZTAS database.

Training the clozapine pharmacist is a key element to the safe dispensing of Zaponex to patients and essential for limiting access of treatment with Zaponex to patients who fulfil the conditions for use. Via the ZTAS training, the clozapine pharmacist qualifies their pharmacy for registration with the ZTAS. Registration of the pharmacy ensures that Leyden Delta can maintain a closed and controlled distribution system for Zaponex, as per regulatory obligations.

Without the clozapine pharmacist's participation in the ZTAS training, the registration of the clozapine pharmacist and their pharmacy cannot be completed and the pharmacy will not be able to order Zaponex from the distributor.

ZTAS training will be organised in co-operation with the hospital/pharmacy. Other healthcare providers/users in the pharmacy or the hospital are welcome to participate in the ZTAS training. Clozapine pharmacists and pharmacy staff can also participate in the ZTAS healthcare provider training via an online course.

All registered healthcare providers have access to the Zaponex product information (SmPC and Patient Information Leaflet), the ZTAS Manual and the ZTAS privacy notice on the ZTAS website.

### 2.2 Registration of healthcare providers

To register with ZTAS, a healthcare provider should submit the applicable Data Form to ZTAS.

Registration forms are available from the ZTAS website at [www.ztas.co.uk](http://www.ztas.co.uk)

Different types of registration forms can be downloaded for various roles in relation to the care for patients registered with the ZTAS (e.g. Consultant, pharmacist, proxy).

Consultant's and pharmacists have the option to register with ZTAS using an **online registration** form. The online registration facility will transfer details in a secure manner to ZTAS. It must however be noted that the online registration is a two-step process. It requires the consultant or pharmacist to first submit an electronically completed Form and thereafter, in a second step to electronically confirm to ZTAS that the information previously completed is accurate and electronically signed (authenticated) by themselves.

The registration of a shared care prescriber is combined with a patient's registration in a 'Shared Care' protocol and should be initiated by the consultant (see [4 Shared Care Registration](#)).

Registration as a healthcare provider with the ZTAS constitutes the healthcare provider's statement of intent to participate in the prescribing, dispensing and monitoring of Zaponex in association with the ZTAS. It is also the healthcare provider's confirmation that he/she agrees to Leyden Delta using their personal information in the context of the Zaponex treatment for their patient(s).

Signing the registration form is regarded as a confirmation of the healthcare provider's understanding of, commitment to, and adherence to their responsibilities vis-à-vis the ZTAS system. These responsibilities vary, depending on the type of healthcare provider registering with ZTAS, and are stated on the relevant registration form.

ZTAS will return a **Registration Confirmation** to all newly registered healthcare providers. The registration confirmation includes a personal username and password allowing access to the ZTAS website.



Healthcare providers registering with ZTAS as a consultant or clozapine pharmacist have end-responsibility for prescribing or dispensing Zaponex to the patients who are registered in association with them in the ZTAS system. These ZTAS-registered healthcare providers are also considered data controllers of the personal data of patients who are treated with Zaponex under their care (see [1.7.1](#)). In this capacity, they are responsible for ensuring that the data they provide to ZTAS is accurate and up to date (see [7 - Maintaining an up-to-date database](#)) and the personal information about the patients under their care is kept secure and confidential.

### 2.3 Sharing information in a care team

Consultants or clozapine pharmacists may wish to involve other members of the care team in the treatment of their patient(s) with Zaponex to enhance continuity of care for their patient(s). This may involve sharing information from ZTAS about their ZTAS-registered patients with other members in the care team

ZTAS supports this by:

- registering supporting staff as proxies
- registering a group email address for standard ZTAS notifications

#### 2.3.1 Proxy registration

Healthcare professionals other than consultants, pharmacists or shared care prescribers should register with ZTAS as proxies. A proxy registration will give supporting members of the care team 'named access' to the details of patients registered in association with the consultant or pharmacist who is responsible for prescribing/dispensing Zaponex to those patients.

To register as a proxy, a **Proxy Data Form** should be used. The form should be completed by the proxy and authorised by the consultant or clozapine pharmacist.

A consultant's or clozapine pharmacist's authorisation is required in order to legitimise a proxy's access to personal information in the ZTAS for patients under the healthcare provider's care.

By authorising a proxy's registration, the consultant or clozapine pharmacist acknowledges that they:

- remain responsible for all tasks related to treatment of patients with Zaponex carried out by the proxy on their behalf
- must periodically review of the list of authorised proxy users, to determine whether continued access for a proxy to the details of patients under their care is necessary and legitimate
- must inform ZTAS within 14 days if a proxy under their authorisation no longer requires access.

ZTAS will return a **Registration Confirmation** to all newly registered proxies to confirm their registration with ZTAS. The registration confirmation includes a personal username and password allowing access to the ZTAS website.

#### 2.3.2 Group email

If a responsible consultant or clozapine pharmacist wishes to share information contained in the ZTAS and/or communications sent by ZTAS concerning their ZTAS-registered patients with other members of the care team, a group email address can be registered with ZTAS.

To register a group email address, the consultant or clozapine pharmacist must provide ZTAS with a completed **Data Sharing Form**.

The Form documents the healthcare provider's awareness of the responsibilities involved in using a group email address and absolves ZTAS/Leyden Delta from liability for data breach and harm to a patient for issues originating from the receipt of the ZTAS patient information on the group email address. Documenting this understanding is necessary, as ZTAS does not have the means to control the legitimacy of access to ZTAS-registered patients' information that is accessed through the group email by other members of the care team.

ZTAS will use the group email only for sending 'standardised ZTAS communications' (e.g. Registration Confirmations, Reminders, Warnings and Alerts). Additionally, as in all situations where email is used as a means of communication between ZTAS and healthcare providers, the patient identifiers are



pseudonymised so that the patient cannot be easily identified without a link to his/her details in the ZTAS system.

Both pseudonymisation and restriction to use a group email address for standard ZTAS communications, help to keep information about patients strictly private and confidential and allow for the sharing of patient information with only those people who need access to it in order to treat patients with Zaponex.

By returning a Data Sharing Form, the responsible healthcare provider confirms to ZTAS that they have appropriate measures in place to guarantee patients' health and the confidentiality of their personal data as received on the group email. These measures include:

- a written policy which addresses who has access to the group email address;
- a process for the periodic review of access rights;
- a definition of the responsibilities of the staff members who can access the information;
- how frequently the email is monitored; and how information will be handled, followed up and escalated.
- the appropriate technical and organisational security infrastructure to prevent unauthorised or unlawful access to or disclosure of the group email address and to prevent accidental loss, alteration or destruction of, or damage to, any patient data sent to the group email address by ZTAS.
- a personal data breach response plan, describing the steps that need to be undertaken in the event of a data security breach incident

Via a Data Sharing Form the healthcare provider acknowledges to ZTAS their responsibility:

- to manage and control access to the group email address
- to ensure the accuracy of any information contained in the ZTAS that may be accessible through the group email,
- to timely notify ZTAS of any changes to (the validity of) the group email address, to details of the patients under the healthcare provider's care, and when access to ZTAS and the ZTAS patient data is no longer required.

It should be noted that regardless of the involvement of additional members of the care team in the treatment of a patient with Zaponex, for ZTAS the responsible healthcare provider remains the first point of contact for anything related to a patient's treatment.



### 3 Patient Registration

Before registering a patient with ZTAS both the consultant responsible for prescribing and treating a patient with Zaponex and the dispensing pharmacist(s) must be registered with ZTAS.

#### 3.1 Eligibility for Zaponex treatment

Prior to starting treatment, the consultant must ensure that the patient is eligible for Zaponex treatment. An important element of the Zaponex controlled access programme is to limit the use of Zaponex to patients for whom the benefits of treatment are expected to outweigh the risks. Zaponex should in principle be used only for patients for whom the indication for use is in accordance with the indications listed in the Zaponex SmPC. For this reason, the indication for Zaponex use must be provided upon a patient's registration with ZTAS.

##### *Off-licence treatment*

We do understand that for some patients, treatment with clozapine may be the best treatment option despite the fact that the indication for use falls outside the approved use conditions as specified in the product information. Treating a patient with Zaponex and his/her registration in an off-licence treatment situation may be accepted by ZTAS but this must be approved by the ZTAS Medical Advisor. The consultant should formally confirm awareness of the risks associated with off-licence Zaponex treatment via an **Off-licence agreement**.

Before a patient may be started on Zaponex a valid blood result is required (see [5.3.1 Initial Result](#)).

#### 3.2 Informing the patient

The healthcare provider registering a patient with ZTAS is responsible for informing the patient (and/or, if the patient is under 18, the patient's parent or legal guardian) of how their personal data will be used by ZTAS, this information should include the transfer of personal data to the Central Non Re-challenge Database (see [3.3.1](#)) if the patient experiences a confirmed 'Red Result'.

The local healthcare organisation's requirements for informing a patient about his/her Zaponex treatment and obtaining the patient's consent should be taken into account in this respect.

ZTAS provides support materials, e.g. the patient handbook, with information for the patient about Zaponex treatment and the ZTAS blood monitoring procedures.

The ZTAS privacy notice and the **Consent Form** outline how Leyden Delta handles a patient's personal information and ensure that it is kept confidential. All of this information, as well as Zaponex product information (PIL) can be used by healthcare providers to provide relevant information about Zaponex treatment and the ZTAS to the patient. The Consent Form can, if necessary, also be used to document their consent to treatment.

The ZTAS privacy notice, Consent Form, and Zaponex product information is available from the ZTAS public website ([www.ztas.co.uk](http://www.ztas.co.uk)). Electronic versions of the patient handbook (in 7 different languages) are available from the secure section of the ZTAS website for ZTAS-registered healthcare providers. Printed copies of the patient handbook or other support materials can be requested from ZTAS

#### 3.3 Registering a patient with ZTAS

To register a patient with ZTAS a **Patient Data Form** must be completed.

The Patient Data Form is available via the ZTAS website ([www.ztas.co.uk](http://www.ztas.co.uk)).

ZTAS offers a choice to submit a patient registration via the **online patient registration** facility on the ZTAS website, or to use a downloadable Patient Data Form.

In all instances, the patient's registration must be confirmed by the patient's (ZTAS-registered) consultant, or a ZTAS-registered pharmacist.

The online patient registration facility will transfer the patient's registration details in a secure manner to ZTAS. It must be noted that if the online registration is a two-step process. It requires a consultant or pharmacist to first submit an electronically completed Form and thereafter, in the second step to



electronically confirm to ZTAS that the information previously completed is accurate and signed by the appropriate ZTAS registered healthcare provider.

The downloaded Patient Data Form must be printed, completed, signed by a ZTAS registered healthcare provider with the appropriate role and sent to ZTAS using in an adequately secure manner.

Regardless of the Data Form option chosen, the patient's registration with ZTAS will only be finalised when ZTAS has received a completed and correctly signed Patient Data Form.

A patient's registration with ZTAS is considered complete when ZTAS has sent a **Registration Confirmation** to the healthcare providers (see section 3.3.2)

For a patient who is switching from another brand of clozapine to Zaponex, ZTAS will request the consultant to also supply a formal request for transfer of monitoring service for the concerned patient. To facilitate this, ZTAS will send the consultant, upon receipt of a completed Patient Data Form, a request to complete a **Transfer Request** for the patient. This would usually be in the format of a link to a WebForm. The Transfer Request Form must be completed by the consultant to authorise the patient's transfer from the previous monitoring service to ZTAS and to obtain the patient's most recent blood-test history from the previous monitoring service.

The consultant should indicate on the Transfer Request Form the date upon which the patient is to be transferred to Zaponex and to ZTAS.

Once ZTAS is in receipt of a fully completed Transfer Request Form\*, this form will be sent to the previous monitoring service to serve as formal notification of the intention to change the patient's clozapine brand to Zaponex.

\* Note: as with other online ZTAS Data Forms, submission of this Form is a two-step process. ZTAS will only receive the information after the confirmation (step 2).

For 'On-treatment' patients transferring from abroad, the monitoring history, most recent clozapine start date and three most recent blood results cannot be obtained from another monitoring service and must be provided to ZTAS directly; without historical information the patient will be registered as a 'New' patient.

### 3.3.1 Checks against the Central Non Re-challenge Database (CNRD)

Restarting clozapine treatment after a patient has previously experienced serious haematological side-effects while being treated with clozapine, regardless of which brand, may seriously jeopardise such a patient's health. For this reason, all manufacturers of clozapine in the UK have jointly set up a system to ensure that such patients will not be exposed to clozapine (of any brand) again. Personal details of these patients are maintained on the CNRD.

ZTAS performs a re-challenge check against the CNRD upon receipt of Patient Data Forms for all patients who are registered as 'New' or 'Interrupted' to clozapine treatment.

If a patient is registered on the CNRD, he/she may not be treated with Zaponex.

In certain situations, patients may be re-challenged with Zaponex, but this can only be done in conjunction with approval from the ZTAS Medical Advisor.

### 3.3.2 Registration Confirmation

Once the Patient Data Form has been processed, the patient is allocated a unique **Patient Identification Number (PIN)** in the ZTAS database. This PIN should be quoted in all communications with ZTAS about the patient.

To confirm a patient's registration, ZTAS will send a **Registration Confirmation** to the consultant and clozapine pharmacist and, if applicable to the shared care prescriber and/or homecare pharmacy.

## 3.4 Initial blood result

Before starting the patient on Zaponex, an initial blood result must be submitted to ZTAS (see [5.2 Blood Data Submission](#)). This initial blood result may be forwarded to ZTAS with the registration form or may be submitted after completion of the patient's registration.

However, blood samples should not be sent to the central laboratory until the patient has been registered on the ZTAS: samples can only be processed by the central laboratory when a patient has



been registered and has been assigned a PIN. All samples sent to the ZTAS central laboratory must be identified by the patient's PIN.

### **3.5 First dispense of Zaponex**

Zaponex can be dispensed to the patient when the patient's registration with ZTAS is complete and when a valid blood result has been recorded in ZTAS (see [5.3 Interpretation blood results](#)).

### **3.6 Patient Card**

When a patient's registration with ZTAS has been completed, a ZTAS Patient Card will be sent to a patient's blood sampling location..

The Patient Card contains relevant, easily understood information for patients about the early symptoms of agranulocytosis and myocarditis, as well as warning signs of other common issues that could negatively affect patients' health. The Patient Card has space for the contact details of the healthcare providers (consultant, clinic and/or pharmacy) who should be contacted by the patient if they experience any of these symptoms. This Patient Card is small enough to fit in a purse or wallet and can also be used to note down a patient's appointments with their care team.

The ZTAS Patient Card can be handed out to a patient when their bloods are taken or the first time their Zaponex is dispensed.

A further supply of Patient Cards can be requested from ZTAS by email ([info@ztas.co.uk](mailto:info@ztas.co.uk)).



## 4 Shared Care Registration

In a shared care situation, the patient is treated with Zaponex in the community. The consultant, a shared care prescriber (e.g. GP) and a hospital and/or community pharmacist work together to manage the care of the patient.

The shared care prescriber performs routine blood monitoring and prescribes Zaponex to the patient. The consultant remains the supervisor of Zaponex treatment. The pharmacist can be either a hospital pharmacist or a community pharmacist.

The procedures for blood monitoring are described in section [5 Blood Monitoring](#).

The shared care prescriber must contact the consultant for any of the following reasons, should they occur, as they may affect the patient's treatment situation:

- treatment break
- amber or red blood result
- the haematological/clinical condition of the patient is not satisfactory or stable
- change in Zaponex dosage
- discontinuation of Zaponex treatment

The consultant is responsible for initiating treatment of a patient in shared care.

A patient is only eligible for Zaponex treatment in shared care when:

- the patient has completed at least one year of Zaponex (clozapine) treatment
- is on a 4-weekly monitoring frequency
- the patient's blood results are stable
- the patient's Zaponex dose is stable

The consultant is responsible for explaining the procedures for blood monitoring and treatment with Zaponex in shared care to the shared care prescriber and for providing them with relevant information about Zaponex and the ZTAS e.g. Zaponex product information, ZTAS manual and the ZTAS privacy notice. This information is available via the ZTAS site and/or will be made available to the shared care prescriber once registered with the ZTAS.

To register a patient under shared care, the consultant and shared care prescriber jointly complete the **Shared Care Data Form**. The consultant should complete the patient and consultant sections of the Shared Care Data Form and should then forward it to the shared care prescriber. The shared care prescriber should review the form, complete his/her details, the details for sampling location, the laboratory and the pharmacy where the patient will have his/her Zaponex medication dispensed. Once completed, the form should be sent to ZTAS.

Upon receipt of the Shared Care Data Form the shared care prescriber will be registered with ZTAS. Following this, the relevant patient will be registered in a shared care situation. Once all the involved parties are registered, ZTAS will confirm the shared care registration to the consultant, shared care prescriber and the clozapine pharmacist.

After being registered with ZTAS, the shared care prescriber will receive a Registration Confirmation with a unique username and password allowing access to the ZTAS website.

If Zaponex is to be dispensed from a new pharmacy, the pharmacist should first register with ZTAS (as clozapine pharmacist) using the Pharmacist Data Form. Once registered, ZTAS will contact the new pharmacist to arrange for ZTAS training (see [2.1 ZTAS training](#)). Participation in ZTAS training is required to obtain authorisation for the purchasing of Zaponex from our Distributor.



## 5 Blood Monitoring

As specified in the Zaponex SmPC, clozapine is known to cause haematological side-effects. One of the most common side-effects is neutropenia, which can develop into a life-threatening condition known as agranulocytosis. For this reason, in the UK, the treatment with clozapine includes mandatory monitoring of the WBC count and differential.

Other known and serious side-effects of clozapine that can be monitored via a full blood count result are eosinophilia (high eosinophil count) and thrombocytopenia (low platelet count).

For the reasons outlined above, patients treated with Zaponex must undergo regular blood-monitoring. The ZTAS monitors four blood count parameters from the full blood count result. The WBC and the neutrophils counts are the parameters of main focus and must be submitted to ZTAS for every result. ZTAS also monitors the eosinophil and the platelets counts if these counts are made available to ZTAS.

A patient's monitoring frequency depends on the patient's blood results, clinical condition and the duration of treatment with Zaponex.

The minimum monitoring frequency requirements are specified in Table 1.

Table 1: Monitoring frequency

Duration of treatment	Monitoring frequency
First 18 weeks	Weekly
19-52 weeks	Fortnightly
> 52 weeks	4-Weekly

### 5.1 Analysis of blood samples

Patients must have their blood samples taken according to the monitoring frequency shown above in Table 1. Depending on the blood-testing arrangement agreed with ZTAS and whether the blood sample is routine or urgent, samples may be analysed by a local laboratory, the central laboratory, or a ZTAS Point of Care blood-testing system (see sections [1.8](#) and [5.2](#)).

### 5.2 Blood data submission

Blood results for ZTAS patients can be submitted to ZTAS in various ways:

- The central laboratory, or any local laboratory which has an arrangement with ZTAS, provides blood results directly to ZTAS electronically (within 24 hours from receipt of the sample in the laboratory).
- For samples that are analysed on a ZTAS Point of Care system, the results are automatically forwarded and uploaded to ZTAS in real-time, provided that a result is accepted by the system as a valid result (see [1.8.3](#)).
- Results may be entered directly onto the ZTAS system by a healthcare provider after they have received the result.
- Any healthcare provider may send a completed **Blood Data Form** or an alternative notification with the relevant details of a Full Blood Count (FBC) result to ZTAS; upon receipt of the information, ZTAS will enter the data on the database on the same (working) day.
- Results should in principle be submitted to ZTAS within 48 hours from analysis of the sample.
- Blood results from urgent samples (i.e. following an initial red result) must be forwarded to ZTAS as soon as possible, but no later than 24 hours after the sample is taken.

### 5.3 Interpretation of blood results

Once blood results are entered on the ZTAS database, the WBC and neutrophils are classified according to the following three-colour band:

- **Green:** A satisfactory result, valid to initiate/continue Zaponex treatment.
- **Amber:** A result which is acceptable for continuation of Zaponex treatment but indicates that extra caution must be exercised. The patient's clinical condition should be closely observed and additional blood tests are required.  
The result may not be acceptable for the initiation of Zaponex treatment.
- **Red:** The result is not satisfactory, and not valid to initiate or to continue Zaponex treatment.



The reference values for the classifications of the blood results and the follow-up actions are summarised in Table 2, Table 3 and Table 4.

ZTAS assigns the colour classification for blood results by analysing the lowest value of each blood parameter (e.g. if the WBC is green but the neutrophil count is red, the overall result is classified as red).

In addition to the WBC and neutrophils, the eosinophil and the platelet values are monitored if provided. These counts do not contribute to the colour classification of the result. If values for these additional parameters are abnormal, the result will be flagged as 'Out of Range' (see [5.4 Out of Range blood results](#)).

### 5.3.1 Initial result

For patients who are already being treated with another brand of clozapine and who transfer into ZTAS (registering as 'On-treatment'), the reference ranges for initial blood results are the same as for routine blood results (Table 3).

For patients who are not treated with clozapine at the time of registration with ZTAS (registering as 'New' or 'Interrupted'<sup>4</sup>), the reference ranges for initial blood result are described in Table 2.

Table 2: Reference values - initial blood result for "New" or "Interrupted" patients

Blood counts (x 10 <sup>9</sup> /L)	Classification	Action
WBC ≥ 4.0 AND neutrophils ≥ 2.5	<b>GREEN</b>	Treatment with Zaponex may be initiated at the discretion of the treating consultant.  Zaponex may be prescribed and dispensed for 7 days.
WBC ≥ 3.5 and < 4.0 AND/OR neutrophils ≥ 2.0 and < 2.5	<b>Intermediate AMBER</b>	Treatment with Zaponex may be initiated when the treating consultant considers the patient eligible.  Additional blood sampling is advised to ensure blood counts are not dropping.
WBC ≥ 3.0 and < 3.5 AND/OR neutrophils ≥ 1.5 and < 2.0	<b>AMBER</b>	The blood result is not valid to initiate Zaponex treatment.  Additional blood sampling is required. Treatment may only be initiated on a Green result or intermediate Amber as described above.
WBC < 3.0 AND/OR neutrophils < 1.5	<b>RED</b>	The blood result is not valid to initiate Zaponex treatment.  Investigate the cause of the abnormal blood result.

The reference values for 'Out of Range' eosinophil and platelet counts are provided in section [5.4](#). It is not advised to initiate Zaponex treatment if an initial blood result for a New or Interrupted-New patient is indicated as 'Out of Range'. However, the treating consultant may decide otherwise.

If Zaponex treatment is initiated following an 'Intermediate Amber' or 'Out of Range' blood result, ZTAS should be informed so that the monitoring records can be updated accordingly.

<sup>4</sup> see [APPENDIX 3 - Patient status definitions](#)



### 5.3.2 Routine results

For patients who are 'On-treatment' with any brand of clozapine blood results are classified according to reference ranges for routine results as outlined in table 3.

Table 3: Reference values for routine blood results

Blood counts (x 10 <sup>9</sup> /L)	Classification	Action
WBC ≥ 3.5 AND neutrophils ≥ 2.0	<b>GREEN</b>	Continue Zaponex treatment.
WBC ≥ 3.0 and < 3.5 AND/OR neutrophils ≥ 1.5 and < 2.0	<b>AMBER</b>	Increase monitoring frequency. (See <a href="#">5.7.1</a> : Increased monitoring frequency). ZTAS starts the Amber Warning procedure.
WBC < 3.0 AND/OR neutrophils < 1.5	<b>RED</b>	STOP Zaponex treatment immediately. ZTAS initiates the Red Alert procedure (see <a href="#">5.7.2</a> ).

If the eosinophil or platelet counts are abnormal on routine blood results, the result will be indicated as 'Out of Range' according to the reference values in section [5.4](#). If a routine blood result is 'Out of Range', it is not advised to continue Zaponex treatment. However, the treating consultant may decide otherwise.

### 5.3.3 Patients with Benign Ethnic Neutropenia

Benign Ethnic Neutropenia (BEN) is defined as: 'The occurrence of neutropenia defined by normative data in Caucasian populations in individuals of other ethnic groups who are otherwise healthy and who do not have repeated or severe infections'.

BEN occurs in 25–50 per cent of people of African descent. Statistically significantly lower WBC and neutrophil counts have been demonstrated in Africans and Afro-Caribbeans compared to Caucasians.

In order to accommodate patients with BEN, ZTAS has adjusted the normal reference ranges for these patients (Table 4). These patients' blood results will automatically be classified according to the alert ranges for BEN.

In order to monitor a patient according to BEN reference ranges, a written confirmation of the BEN diagnosis is required from a consultant haematologist. To facilitate the approval of BEN monitoring, ZTAS-registered healthcare providers can download the ZTAS **Confirmation of Benign Ethnic Neutropenia Monitoring Criteria Approval Form** from the secure section of the ZTAS website.



Table 4: Reference values for patients with Benign Ethnic Neutropenia


Blood Counts (x 10 <sup>9</sup> /L)	Classification	Action
WBC ≥ 3.0 AND neutrophils ≥ 1.5	<b>GREEN</b>	Continue Zaponex treatment.
WBC ≥ 2.5 and < 3.0 AND/OR neutrophils ≥ 1.0 and < 1.5	<b>AMBER</b>	Increase monitoring frequency. (See <a href="#">5.7.1</a> ).  ZTAS starts the Amber Warning procedure.
WBC < 2.5 AND/OR neutrophils < 1.0	<b>RED</b>	STOP Zaponex treatment immediately.  ZTAS initiates the Red Alert procedure (see <a href="#">5.7.2</a> ).

For patients monitored according to BEN ranges, the 'Out of Range' values for eosinophil and platelet counts and the treatment advice are the same as for routinely monitored patients (see 5.4).

#### 5.4 Out of Range blood results

Discontinuation of Zaponex treatment is recommended when a patient develops eosinophilia and/or thrombocytopenia. The ZTAS system indicates that eosinophil and/or platelet counts fall outside acceptable ranges with the 'Out of Range' symbol according to following reference limits:

Table 5: Reference ranges for 'Out of Range' blood results

 Out of Range	Eosinophils/ platelets (x10 <sup>9</sup> /L)	Action
High eosinophils	> 1.0 - Pre-treatment > 3.0 - On-treatment	Initiation / continuation of Zaponex treatment is not recommended.  Increase monitoring frequency. (See section <a href="#">5.7</a> ).
Low platelets	< 50	ZTAS starts the Out of Range Warning procedure.

In accordance with the Zaponex SmPC, initiation and/or continuation of Zaponex treatment is not recommended in case of 'Out of Range' eosinophils and/or platelets values. Any decision regarding a patient's treatment with Zaponex is at the discretion of the treating consultant. Additional blood testing is advised on a twice weekly basis until results have stabilised in the following ranges (Table 6):

Table 6: Reference limits for (re)starting Zaponex following an 'Out of Range' blood result

Eosinophils < 1.0	and	Platelets ≥ 50
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For 'New' and 'Interrupted-New' patients<sup>5</sup>, Zaponex therapy should be started only after blood results have stabilised in the ranges as outlined in Table 6 above.

<sup>5</sup> See [APPENDIX 3 – Patient status definitions](#)



## 5.5 Alerts, Warnings and Courtesy reminders

All patients' blood results should be timely entered onto the ZTAS database (see [5.2 Blood data submission](#) for timelines). The ZTAS generates Alerts, Warnings and Courtesy Reminders to help consultants and pharmacists manage their patients on Zaponex.

The ZTAS Alerts, Warnings and Reminders are sent to a patient's consultant, clozapine pharmacist and, if applicable, to the general practitioner (in shared care) and/or HomeCare or community pharmacy dispensing Zaponex to the patient. ZTAS will send the standard communications by email. When appropriate, healthcare providers are also contacted by phone. [Section 2.3](#) explains how ZTAS supports the sharing of information from ZTAS registered patients within the care team.

## 5.6 Dispensing Zaponex

Zaponex may be prescribed only when the following criteria have been met:

- a blood sample is taken from the patient and the result qualifies for Zaponex dispensing (see sections [5.1](#) and [5.3](#)).
- the treating consultant has reviewed the result and made a clinical assessment of the patient. If there are signs of infection, refer to section [5.7 - Increased monitoring frequency](#).
- the Zaponex prescription may not exceed the duration of the monitoring frequency (see Table 7 below).

The pharmacist may only dispense Zaponex to a patient if:

- a valid Zaponex prescription from a ZTAS-registered prescriber is available.
- a valid blood result is available.

A blood result is considered valid for dispensing when:

- the colour classification of the blood result justifies the dispensing of Zaponex (see [5.3](#)).
- the analysis date of the blood result falls within the time limit of the monitoring frequency (see Table 7 below).

The first prescription of Zaponex may be dispensed only if the initial blood result is not older than 10 days and may not exceed 10 days from the date of the result. For example, an initial blood result dated 1 August is valid to start Zaponex treatment until 10 August. A new blood result will be required on 10 August for further dispensing.

The pharmacist should dispense Zaponex to the patient in accordance with the monitoring frequency (see Table 7).

For weekly and fortnightly monitored 'On-treatment' patients, a result is valid for dispensing from the analysis date of the blood result until 7 days beyond the monitoring frequency. If the patient's monitoring frequency is 4-weekly the maximum dispensation may not exceed the monitoring frequency + 14 days.

*Table 7: Zaponex dispensing in relation to treatment - Validity period of a blood result*

Duration of treatment	Monitoring frequency	Maximum Zaponex supply
1-18 weeks	Weekly	7 + 7 days
19-52 weeks	Fortnightly	14 + 7 days
> 52 weeks	4-Weekly	28 + 14 days

The pharmacist is responsible for maintaining a record of Zaponex dispensations to patients.

The Dispense List on ZTAS can help facilitate this practice.

The Dispense List function in ZTAS provides the option to register a patient's Zaponex dose with each result qualifying for dispense. Pharmacies should instruct their staff on how to populate and use the Zaponex dosing information submitted to ZTAS via the Dispense List.



## 5.7 Increased monitoring frequency

Certain situations require that the monitoring frequency be increased.

### 5.7.1 Twice per week monitoring

The monitoring frequency should be increased to *twice per week* if:

- a patient develops symptoms of infections and/or:
- a new blood result is received for a patient by the ZTAS system which prompts the system trigger an alert for one of the below blood result abnormalities (Warnings):
  - a single drop or downward trend in WBC values is detected for a weekly monitored patient
  - the new result is an Amber result
  - the eosinophil and/or platelet counts of the result is 'Out of Range'.

If any of the above mentioned situations is applicable, the patient's physician is advised to assess the clinical status of the patient and request an additional blood sample. The monitoring frequency should be increased to twice weekly until the symptoms have abated and the blood results have stabilised within green ranges.

Based on the assessment of the patient's general health and result history, the consultant should decide if continuation of Zaponex treatment is appropriate.

In case a patient has not yet started with Zaponex treatment and an Amber or Out of range blood result was received for the patient, the initiation of Zaponex should be carefully considered by the consultant (see sections [5.3.1](#) and [5.4](#))

#### **Symptoms of Infection**

If symptoms of possible infection (e.g. flu-like symptoms, fever, mouth ulcers, sore throat, tiredness, weakness or other signs of infection) are present but the clinical examination and the differential blood count are normal, the patient may continue with Zaponex. It is advisable, however, to increase the monitoring frequency until the symptoms have subsided.

#### **Single Drop or Downward Trend in WBC counts**

ZTAS signals for a fast decrease of the WBC counts in a patient's recent blood result history for (On-treatment) patients who are monitored in a weekly frequency.

When a Single Drop (compared to the previous result) or a Downward Trend (compared to the three previous results) in the WBC count of more than  $3.0 \times 10^9 /L$  is detected in a patient's this is indicated on the ZTAS system by a symbol with a black downward arrow with the corresponding blood result. For weekly monitored patients, a Single Drop/ Down Ward Trend Warning will be raised if the latest result has both a 'downward arrow' **and** a WBC count value below  $7.0 \times 10^9/L$  whilst still in green ranges. The Single Drop/ Down Ward Trend Warning will be sent to the patient's healthcare providers. The consultant is advised by ZTAS to assess the patient's general health and determine whether or not an increase of the monitoring frequency to twice weekly is necessary until the blood results have stabilised.

#### **Amber result**

Upon receipt of a result classified by the ZTAS system as Amber, an 'Amber Warning' will be sent to both the consultant and the clozapine pharmacist to inform them of the amber result.

The Amber Warning will contain the advice to carry out twice weekly blood testing and requests the consultant to consider whether continuation of Zaponex treatment continues to be appropriate.

In case ZTAS receives an Amber result for a patient who has not yet started Zaponex (i.e. the ZTAS patient status is a pre-treatment status), an Amber Warning will be sent and the patient's healthcare providers will be contacted by ZTAS by telephone.

#### **Out of Range eosinophil and/or platelet counts**

When an 'Out of Range' eosinophil and/or platelet count is received (see [5.4](#)) the ZTAS system will flag the patient's record and the applicable result with the 'Out of Range' symbol. The 'Out of Range' Warning will be sent to the patient's healthcare providers, to inform them of the 'Out of Range' result and to advise twice weekly blood monitoring.



### 5.7.2 Daily monitoring - Red result

If a blood result for an On-Treatment patient is classified as 'Red', Zaponex must be stopped immediately.

Upon receipt of a 'Red result', ZTAS will:

- immediately contact the consultant to notify him/her about the red result, to discuss the further management of the patient and to initiate the **Red Alert procedure**:
- also, the clozapine pharmacist, and if applicable, the shared care prescriber, will be contacted to notify that clozapine treatment must be stopped immediately.
- The '*Red Alert*' and '*Red Alert Guidelines*' will be sent to the patient's healthcare providers to explain the procedure for further monitoring.

#### **Red Alert procedure**

The consultant must contact the patient immediately and:

- request that the patient comes to the clinic and hands over all Zaponex tablets
- arrange for additional blood testing
- inform the patient to watch for signs of infection (i.e. sore throat, fever). If there are signs of infection, the patient must urgently contact the consultant
- observe the patient for secondary infections
- if there is a (secondary) infection, or when the neutrophil count decreases below  $0.5 \times 10^9/L$ , the consultant should consult a haematologist to discuss the appropriate treatment regimen. The consultant is advised to follow the *Red Alert guidelines*, as provided by ZTAS, which are sent together with the *Red Alert*.

A patient who experiences a 'Red result' should be kept under close clinical surveillance and daily blood monitoring. The results of the urgent blood tests must be submitted to ZTAS within 24 hours of availability.

The patient's status and results will be checked by ZTAS on a daily basis during the Red Alert procedure. Results following the initial 'Red result' will determine the course of further action with regards to the patient's Zaponex treatment.

Non-compliance to instructions in the Red Alert procedure may jeopardise your patient's health.

#### **Non-Rechallengeable procedure**

The Non-Rechallengeable procedure begins when the initial 'Red result' has been confirmed by a second 'Red result'. ZTAS contacts the patient's consultant again to discuss the result, to confirm the discontinuation of Zaponex treatment and to inform the consultant that the patient should not be re-challenged with (any brand of) clozapine.

ZTAS will submit the patient's details to the Central Non-Rechallengeable Database (CNRD). The patient's healthcare providers will receive the notification 'Reminder – Non-Rechallengeable patient'. The reminder provides information about the follow-up monitoring procedure for a Non-Rechallengeable patient.

During the Non-Rechallengeable procedure, daily blood tests are required until the blood results have returned to normal (green) values (see Table 3 and Table 4). All blood results should be forwarded to ZTAS. Once stable in 'green' ranges, the patient must continue weekly, post-treatment monitoring for the 4 weeks (see [6.2.2](#)).

ZTAS may decide to start the Non-Rechallengeable procedure when:

- follow-up results are not provided within 24 hours of the initial 'Red result', or when
- follow-up results are indicative of abnormality, though not in 'Red' ranges.



### Re-starting Zaponex Treatment following a non-confirmed red result

Zaponex may be re-started for a patient when the following conditions are met:

- the (initial) red result was not confirmed by another abnormally classified blood result.
- the red result may be considered a single, isolated abnormal blood result. In this case, the red result cannot have been preceded by an abnormally classified blood result in the previous three months.
- the initial red result is followed-up by two daily, consecutive blood results classified as 'green'.
- the first of these two 'green' results must have been provided to ZTAS within 24 hours from the red result. The second green result must follow approximately 24 hours after the first green result.

Any other situation in which a consultant would like to re-start a patient on Zaponex should be discussed with the ZTAS Medical Advisor. If there is an intention to restart a patient's Zaponex treatment following a red result, daily blood monitoring should be maintained until blood results have stabilised in green ranges (i.e. two consecutive green results in a daily frequency).

### 5.8 Overdue blood results

All blood results should be entered onto the ZTAS database within 2 working days from the date of analysis. Blood results that have not been submitted to ZTAS in a timely manner are classified as 'overdue'. If a blood result is 'overdue' the following safety procedures are initiated:

Table 8: Follow-up actions by ZTAS for missing blood results

A blood result is not in the ZTAS	Action
at the 'expected next test date'	The late flag <b>L</b> is displayed with the patient's record until a new blood result has been entered.
7 days after the expected test date	<i>Reminder – Late Results</i> is sent to healthcare providers. For weekly and fortnightly monitored patients, the previous result is no longer valid for dispensing Zaponex to the patient. ZTAS may contact healthcare providers by telephone to discuss missing follow-up information and/or change the patient status to Interrupted.
14 -28 days after the expected test date	Additional weekly Reminders – Late Results are sent to healthcare providers. The previous result is no longer valid for dispensing Zaponex to the patient. ZTAS contacts healthcare providers by telephone to discuss missing follow-up information. Change of patient status to Interrupted

Upon receipt of a *Reminder – Late results*, healthcare providers are expected to provide ZTAS with follow-up information for the patient(s) concerned. If no response is received by ZTAS following the first Reminder, ZTAS will send a maximum of 3 additional weekly reminders after the initial reminder. ZTAS contacts healthcare providers by telephone to discuss missing follow-up information. If no additional follow-up information is provided, ZTAS will modify the patient status to "Interrupted". To restart Zaponex treatment, the patient should be re-registered with ZTAS.

ZTAS must be informed if the patient refuses to co-operate with Zaponex treatment according to the ZTAS guidelines as outlined in this manual (see [6.2 Treatment Discontinuation](#)).

If no further monitoring information can be submitted to ZTAS because of a change in the patient's treatment status, this should also be reported to ZTAS.



## 6 Changes to Zaponex Treatment

### 6.1 Treatment break

A treatment break is defined as a period in which a patient has stopped taking his/her Zaponex medication for any reason.

Before re-starting Zaponex treatment, the dosage of Zaponex and the monitoring frequency applicable before the treatment break, should be reviewed.

For advice on re-starting Zaponex therapy, please refer to the Zaponex SmPC (section 4.2 Posology and method of administration) and the Zaponex Dosing Schedule Card. Both are available from the ZTAS website.

To determine the appropriate monitoring frequency after a treatment break, the duration of the treatment break and the monitoring frequency before the treatment break should be considered. Table 9 provides the list of monitoring frequencies applicable for re-starting Zaponex treatment after a treatment break.

The duration of a treatment break would be the time period without Zaponex medication, calculated from the last Zaponex dose that was taken at the patient's usual time. For example, if a patient on twice daily dosing has omitted his evening dose, the treatment break is to be calculated from the time of the last morning dose taken by the patient.

Table 9: Monitoring frequency after treatment break

Monitoring frequency	Duration treatment break	Monitoring frequency after treatment break
Weekly	≤ 3 days	Weekly, continue 18 weeks period
Weekly	> 3 days but ≤ 1 week	Weekly, continuing the 18 weeks period; patient must have at least 6 weeks of weekly monitoring prior to a decrease of the monitoring frequency to fortnightly
Weekly	> 1 week	Weekly, restart 18 weeks period
Fortnightly	≤ 3 days	Fortnightly, continue
Fortnightly	> 3 days but ≤ 4 weeks	Weekly monitoring for 6 weeks, then continue Fortnightly
Fortnightly	> 4 weeks	Weekly, restart 18 weeks period
4-Weekly	≤ 3 days	4-Weekly, continue
4-Weekly	> 3 days but ≤ 4 weeks	Weekly monitoring for 6 weeks, then continue 4-Weekly
4-Weekly	> 4 weeks	Weekly, restart 18 weeks period, after 18 weeks, switch to 4-Weekly

If the ZTAS database indicates that a treatment break of more than 1 week (for patients on weekly monitoring), or more than 4 weeks (for patients on fortnightly or 4-weekly monitoring) has occurred, the patient's healthcare providers will be contacted. If no further follow-up information can be provided, the patient status will be changed to "Interrupted".

Before Zaponex treatment can be re-started for a patient with an inactive treatment status in the ZTAS (see [Appendix 3](#), for patient status definitions), the patient must be re-registered. A new registration form should be submitted to ZTAS.

For a patient whose treatment has stopped, see section [6.2 Treatment Discontinuation](#).



## 6.2 Treatment discontinuation

If a patient's Zaponex treatment is discontinued, ZTAS must be informed within 24 hours from the actual discontinuation. ZTAS should also be informed about the reason for stopping Zaponex treatment (see Table 10). A notification about the discontinuation of a patient from Zaponex treatment should be sent/confirmed to ZTAS in writing.

Table 10: Reasons for stopping Zaponex

Reasons for stopping Zaponex	ZTAS Patient Status
Discontinuation for non-haematological reasons	Discontinued
Discontinuation because of a confirmed red result	Non-Rechallengeable
Patient is transferred to another brand of clozapine	Transferred
Patient died	Deceased

After discontinuation of Zaponex therapy, blood monitoring must be continued for an additional 4 weeks after the last dose of Zaponex.

The follow-up monitoring procedure for patients who have stopped Zaponex due to non-haematological reasons, or following an unconfirmed red result is described in [6.2.1 Discontinuation for non-haematological reasons](#).

The discontinuation procedure for patients who have stopped Zaponex following a confirmed 'Red result' is described in [6.2.2 Discontinuation for haematological reasons](#)

Patients who have transferred to another brand of clozapine do not require follow-up blood monitoring.

### 6.2.1 Discontinuation for non-haematological reasons

The patient status 'Discontinued' is used for patients whose Zaponex treatment was stopped for reasons other than a confirmed red result.

The number of additional blood results expected by ZTAS depends on the monitoring frequency at the time of treatment discontinuation:

- for patients with a weekly monitoring frequency, 4 additional weekly blood results must be forwarded to ZTAS.
- for patients with a fortnightly monitoring frequency, 2 additional blood results must be submitted to ZTAS within 4 weeks after the discontinuation.
- for patients with a 4-weekly monitoring frequency, 1 additional blood result must be submitted 4 weeks after the actual discontinuation. The patient should discontinue at the end of the 4-weekly interval and then have a blood test. The final test should follow one month later. Discontinuing treatment just before a blood test is not recommended.

### 6.2.2 Discontinuation for haematological reasons

Patients who discontinue Zaponex treatment due to a confirmed 'Red' result should not be re-challenged with (any brand of) Clozapine. The patient status Non-Rechallengeable is displayed on the ZTAS database and the patient enters the **Non-Rechallengeable procedure** (see [5.7](#)).

The Non-Rechallengeable procedure requires daily blood monitoring until the values have returned to 'green' ranges. These results must be provided to ZTAS within 24 hours of analysis.

Once the results have stabilised, follow-up monitoring is required for 4 weeks at a weekly monitoring frequency. All blood results should be forwarded to ZTAS.



### 6.2.3 Discontinuation with an increased monitoring frequency

If patients discontinue Zaponex treatment whilst being monitored on a twice weekly basis, the follow-up blood monitoring should also continue on a twice weekly basis until results are in stable ranges (see [Table 3](#) for 'green ranges for WBC and neutrophil counts, [Table 5](#) for eosinophil and platelet counts).

Twice weekly monitoring after discontinuation is advised in the following circumstances:

- a WBC and/or neutrophil count classified as 'Amber'
- symptoms of infection
- 'Out of Range' eosinophil and/or platelet counts.

For patients who discontinue Zaponex treatment following an unconfirmed red result, daily monitoring should be maintained until the results have returned to 'green' ranges. Thereafter, 4 additional weekly blood results must be forwarded to ZTAS.

### 6.3 Patient relocation

When a patient moves to another area within the UK, ZTAS may be consulted to facilitate the transfer of the patient to another treatment location. The patient's physician and/or pharmacist wishing to relocate the patient should contact the physician or pharmacist at the new location directly. This discussion should address the relocation of the patient and to ensure that the healthcare providers at the new location assume responsibility for the treatment and monitoring of the patient.

ZTAS should be informed when a patient is being relocated to a different ZTAS-registered location and/or to new healthcare providers. The notification should include the written approval of both the old and the new healthcare providers and should state the actual date that the change is to take effect. Once updated in ZTAS, the patient's (electronic) ZTAS records will automatically be forwarded to the new healthcare providers at the new treatment location.



## 7 Maintaining an up-to-date database

The ZTAS database must be properly maintained and kept as accurate as possible in order to ensure that:

- patients are safely treated with Zaponex,
- the patients and their blood results can be efficiently monitored by ZTAS, and
- the personal information (including health care information) of patients remains accurate

To help achieve this, healthcare providers shall inform ZTAS as soon as reasonably practicable, but at least within a period of 30 days, of any changes to:

- registration details held by ZTAS
- specific details for their patients

Stricter notification timelines apply to changes which have a higher potential risk for personal data breach. Healthcare providers shall notify ZTAS within a period of 14 days about any changes to the following data:

- registration details for their proxies
- their registered group email address.

Healthcare providers shall also notify ZTAS, as soon as reasonably practicable, whenever they discover errors or missing information on the ZTAS database. Relevant documents regarding the patients shall also be forwarded to ZTAS.

The **consultant** is responsible for maintaining accurate details in ZTAS for:

- his/her personal registration details
- details for his/her proxy(ies).
- details for his/her patients' registration and treatment status

The **pharmacist** is responsible for maintaining accurate details in ZTAS for:

- his/her personal registration details
- errors in patient blood results and/or dispensing information
- for **clozapine pharmacists**; details for the pharmacy proxy(ies).

The **shared care prescriber** is responsible for maintaining accurate details in ZTAS for:

- his/her personal registration details
- registration details for patients registered to him/her in a shared care environment

Healthcare providers should immediately inform ZTAS if they receive any complaint, notice or communication which relates directly, or indirectly to the processing of a ZTAS registered patient's information, or to the healthcare provider's compliance with the applicable data protection legislation and its data protection principles in relation to any ZTAS registered patient's information, including if it should become aware of any actual or suspected unauthorised or unlawful access to or disclosure of personal data (see [1.6](#)). Our Data Protection Officer can be contacted directly via [dataprotectionofficer@ztas.co.uk](mailto:dataprotectionofficer@ztas.co.uk).

### 7.1 Change of details

A request for change of data must be submitted to ZTAS in writing. ZTAS will accept changes to patient information from any member of care team involved with a patient's treatment. This is, provided that we can establish a legitimate connection to the patient and the responsible consultant or clozapine pharmacist on behalf of whom the change is provided (e.g. associations of the user in the ZTAS, or from letter head or email signatory). The '**Change to Patient Details Form**' can be used for this purpose. The form is available the ZTAS website as a WebForm. This will ensure the changes to patient details are transferred to ZTAS in a secure manner.

It must be noted that the use of WebForms is a two-step process. It requires a healthcare provider to first submit an electronically completed Form and thereafter, in the second step to electronically confirm to ZTAS that the information previously completed is accurate and signed by a ZTAS registered healthcare provider.



Changes submitted to ZTAS are processed on the database by ZTAS. Once actioned, the changes can be reviewed on the ZTAS system.

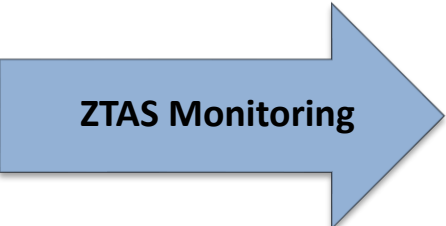

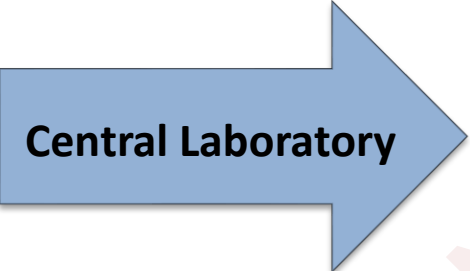

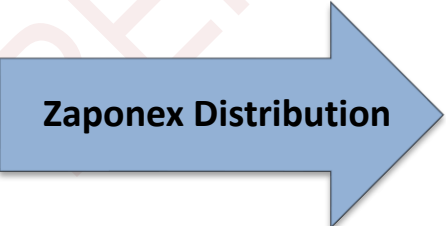

## 7.2 De-registration

Healthcare providers who are no longer involved in prescribing and/or dispensing Zaponex to patients should de-register themselves from the ZTAS database. A consultant or a clozapine pharmacist can be de-registered from ZTAS after their patients are transferred to another consultant or clozapine pharmacist. A healthcare provider who wants to de-register should inform ZTAS of this in writing (e.g. by email).

Healthcare providers are responsible for ensuring that the information about their patients held on the ZTAS system remains confidential. Healthcare providers who have registered proxies are responsible for periodically reviewing their list of authorised proxies to determine whether their continued access to the ZTAS database is necessary and legitimate. Where their continued access is no longer necessary, healthcare providers shall, as soon as reasonably practicable and in any event within 14 days, inform ZTAS in writing of this and provide ZTAS with the necessary details to de-register those proxies.



## APPENDIX 1 – Contact information

<div style="text-align: center;">  <p><b>ZTAS Monitoring</b></p> </div> <ul style="list-style-type: none"> <li>• All communications relating to ZTAS, including requests for medical information, and reports of adverse events on Zaponex treatment,</li> <li>• For the ordering of Zaponex (clozapine) customer support materials (e.g. patient cards or patient notes folders).</li> <li>• Out of hours contact telephone number for emergency situations</li> </ul>	<div style="text-align: center;">  </div> <p>Contact: <b>ZTAS Office</b>          Telephone: 020 7365 5842 (24 hours)          E-mail: <a href="mailto:info@ztas.co.uk">info@ztas.co.uk</a>          Internet: <a href="http://www.ztas.co.uk">www.ztas.co.uk</a></p> <p>Questions or concerns about the handling of personal information by ZTAS can also be addressed directly to <a href="mailto:dataprotectionofficer@ztas.co.uk">dataprotectionofficer@ztas.co.uk</a></p>
<div style="text-align: center;">  <p><b>Central Laboratory</b></p> </div> <p><b>For all enquiries relating to:</b></p> <ul style="list-style-type: none"> <li>• supply of haematological kits, including needle holders, needles, tubes and post/packaging materials</li> <li>• Blood request forms and pre-printed patient labels</li> <li>• Clozapine assay supplies and results</li> <li>• Courier collections</li> </ul>	<div style="text-align: center;">  </div> <p>Contact: <b>Magna Laboratories Ltd</b>          Telephone: <b>01989 763 333</b>          E-mail: <a href="mailto:info@magnalabs.co.uk">info@magnalabs.co.uk</a>          Internet: <a href="http://www.magnalabs.co.uk">www.magnalabs.co.uk</a>          Results: <a href="http://www.bloodresult.co.uk">www.bloodresult.co.uk</a></p> <p>Orders for new supplies can also be made online via <a href="http://www.magnalab.co.uk">www.magnalab.co.uk</a> and the <a href="http://www.ztas.co.uk">www.ztas.co.uk</a></p>
<div style="text-align: center;">  <p><b>Zaponex Distribution</b></p> </div> <p>To place orders for Zaponex (clozapine) and any order enquiries.</p>	<div style="text-align: center;">  </div> <p>Contact: <b>Alloga (UK)</b>          Telephone: 01773 441 702          Telephone: 01773 441 700 (EDI assistance)          Fax: 01773 810644          E-mail: <a href="mailto:allogauk.orders@alloga.co.uk">allogauk.orders@alloga.co.uk</a></p>



## APPENDIX 2 – Abbreviations and terminology

<b>Agranulocytosis</b>	A condition indicated by a very low (absolute) neutrophil and/or WBC count (neutrophils $< 0.5 \times 10^9/L$ and/or WBC $< 1.0 \times 10^9/L$ ). Agranulocytosis is a known side effect from clozapine and could lead to a life-threatening situation for a patient. This side effect is the reason for the requirement of blood monitoring with Zaponex treatment.
<b>Alloga</b>	Alloga UK Ltd – Distributor of Zaponex® in the UK.
<b>BEN</b>	Benign Ethnic Neutropenia; the occurrence of neutropenia, defined by normative data in white populations, in individuals of other ethnic groups who are otherwise healthy and who do not have repeated or severe infections
<b>BloodResults®</b>	A web-based reporting system used by Magna Laboratories for the full blood count and clozapine assay results of ZTAS registered patients; the results reported via BloodResults are online accessible for consultants and clozapine pharmacists associated with a patient in the ZTAS via <a href="http://www.bloodresult.co.uk">www.bloodresult.co.uk</a> .
<b>Central laboratory</b>	The laboratory associated with ZTAS that centrally analyses blood samples from patients treated with Zaponex. Magna Laboratories Ltd in Ross-on-Wye.
<b>Change request</b>	Request written by a healthcare provider for a change of details in the ZTAS system
<b>Clozapine pharmacist</b>	Pharmacist registered with ZTAS, who is the primary point of contact for ZTAS at that pharmacy.
<b>CNRD</b>	Central Non-Rechallenge Database; Database developed and owned by CNRD 2002 Ltd; a company represented by marketing authorisation holders (MAHs) for clozapine in UK. The purpose of the CNRD is sharing data on patients who experienced a confirmed red result whilst treated with clozapine between the MAHs to prevent a re-challenge with clozapine and jeopardising such patients' health.
<b>Data Protection Legislation</b>	Applicable data protection legislation: i.e. General Data Protection Regulation (GDPR) and Data Protection Act 2018 (UK's implementation of GDPR).
<b>Eosinophilia</b>	A condition indicated by a high eosinophil count (eosinophils $> 3.0 \times 10^9/L$ ; as based on Zaponex SmPC), Eosinophilia is a known and common side effect from clozapine.
<b>FBC</b>	Full Blood Count; the relevant blood test for ZTAS blood monitoring
<b>GDPR</b>	EU General Data Protection Regulation 2016/679; in the UK implemented via Data Protection Act 2018 (UK-GDPR).
<b>GMC</b>	General Medical Council: professional regulatory body for physicians. The GMC maintains the professional register for all qualified physicians in the UK.
<b>GMC number</b>	Professional registration number for a qualified physician in the UK. The GMC number is used by ZTAS as the unique identifier for a consultant psychiatrist or general practitioner in the ZTAS system.
<b>GP</b>	General Practitioner
<b>GPC</b>	General Pharmaceutical Council: professional regulatory body for pharmacists and pharmacy technicians in England, Scotland and Wales. The



	GPC maintains the professional register for qualified pharmacists in England, Scotland and Wales.
<b>GPC number</b>	Professional registration number for a qualified pharmacist in England, Scotland and Wales. The GPC number is used by ZTAS as a unique identifier for a pharmacist in the ZTAS system.
<b>Healthcare provider</b>	The consultant psychiatrist, pharmacist, shared care prescriber registered with ZTAS with primary responsibility for the prescribing/ dispensing of Zaponex to a patient.
<b>Leyden Delta</b>	Leyden Delta B.V. – Marketing Authorisation Holder for Zaponex®.
<b>Magna Laboratories</b>	Central laboratory for the analysis of ZTAS blood samples
<b>MHRA</b>	Medicines and Healthcare Products Regulatory Agency
<b>MPOC</b>	Main Point of Contact for ZTAS (MPOC). When a Trust/Health Board participates in the ZTAS POCT service (see section <a href="#">1.8.3</a> ), it is expected the Trust/Health board nominates one person among the members of their POCT service who can act as a central point of contact for ZTAS in case of any issues or concerns. This person should have day-to-day involvement in the clozapine services.
<b>NEQAS</b>	National External Quality Assurance Scheme; an independent organisation with the sole purpose of assessing and maintaining the integrity of diagnostic testing equipment. Analysing instruments registered in this scheme are periodically assessed and their analysis performance is compared with similar analysing instruments registered in the scheme.
<b>Neutropenia</b>	A condition indicated by a low absolute neutrophil count (neutrophils $0.5 - 1.5 \times 10^9/L$ ), Neutropenia is a known and common side effect of clozapine.
<b>Neutrophils</b>	Absolute neutrophil count (ANC)
<b>Physician</b>	A medically trained person; e.g. consultant (specialist in psychiatry or another relevant treatment area) responsible for supervision of Zaponex treatment) or a shared care prescriber (e.g. general practitioner)
<b>Personal data breach</b>	any security incident that has affected the confidentiality, integrity or availability of personal data. <i>Personal data breaches can include:</i> <ul style="list-style-type: none"> <li>• access by an unauthorised third party</li> <li>• deliberate or accidental action (or inaction)</li> <li>• sending personal data to an incorrect recipient;</li> <li>• computing devices containing personal data being lost or stolen</li> <li>• alteration of personal data without permission, and</li> <li>• loss of availability of personal data.</li> </ul>
<b>PIL</b>	Zaponex Patient Information Leaflet; product information leaflet included in the Zaponex packs. It is written for patients and gives information about taking or using Zaponex.
<b>PIN</b>	Patient Identification Number: unique identification number for a patient who is registered with ZTAS
<b>Platelets</b>	Platelet count



<b>POCT coordinator</b>	Senior healthcare professional with overall responsibility for ensuring the correct working of POCT within a trust/board
<b>PNI/ PSNI</b>	Pharmaceutical Society Northern Ireland: professional society for pharmacists in Northern Ireland. The PSNI maintains the professional register for qualified pharmacists in Northern Ireland.
<b>PNI number</b>	Professional registration number for a qualified pharmacist in Northern Ireland. The PNI number is used by ZTAS as a unique identifier for a pharmacist in the ZTAS system.
<b>POCT</b>	Point of Care Testing: any analytical test performed for a patient by a healthcare professional outside the conventional laboratory setting. In the context of ZTAS it refers to point of care blood testing. The analysis equipment is operated by trained non-laboratory staff.
<b>POCT coordinator</b>	Senior healthcare professional with overall responsibility for ensuring the correct working of POCT within a Trust/Board
<b>Pochi</b>	Point of care Haematology instrument - A small, compact, and fully automated blood testing instrument that has been developed for the analysis of blood samples outside a laboratory environment. The instrument is specifically designed for 'near patient' testing of blood samples and provides a FBC with a 3 part differential (1. neutrophils; 2. lymphocytes; and 3. A mix of basophils, eosinophils and monocytes). In the ZTAS POCT service the Sysmex Poch-100i analyser device is used to analyse blood samples.
<b>POCT operator</b>	A ZTAS registered healthcare provider or proxy who has been trained in the proper use of a ZTAS POCT instrument.
<b>Proxy</b>	Person fulfilling tasks for ZTAS on behalf of a pharmacist or a consultant
<b>Pseudonymisation</b>	A procedure by which direct identifying personal information in a data record or communication is replaced with a pseudonym, and/or indirect information. Pseudonymisation provides a means for processing of personal data in such a way that the data can no longer be attributed to a specific data subject without the use of additional information. For ZTAS registered patients, the PIN is used as the pseudonym. Indirect patient identifiers as Date of Birth and/or a patient's initials are used as secondary identifiers, to safeguard data integrity.
<b>SmPC</b>	Summary of Product Characteristics; The basis of information about a product for healthcare providers on how to use the product safely and effectively.
<b>Thrombocytopenia</b>	A condition indicated by a low Platelets count (Platelets < 50 x10 <sup>9</sup> /L; as based on Zaponex SmPC). Thrombocytopenia is a known but rare side effect from clozapine.
<b>UKAS</b>	United Kingdom Accreditation Service: sole accreditation body recognised by British government to assess the competence of organisations that provide certification, testing, inspection and calibration services. <i>E.g. accredits medical laboratories according to ISO 15189 standards</i>
<b>WBC</b>	White Blood Cell count
<b>Zaponex®</b>	The proprietary brand name of clozapine marketed in the UK by Leyden Delta B.V.



Zaponex Treatment Access System

- ZTAS®** Zaponex Treatment Access System: Monitoring system for patients treated with Zaponex.
- ZTAS user ID** Unique identifier for a healthcare provider in the ZTAS system.
- ZTAS POCT System** A Point of Care blood testing system that consists of the Sysmex Poch-100i haematological analyser attached to a computer running the dedicated ZTAS POCT (client end) software. A ZTAS POCT system is used to test blood samples. After validation by the ZTAS POCT software, results are automatically uploaded onto the ZTAS system.

REFERENCE ONLY



## APPENDIX 3 – Patient status definitions

The various ZTAS patient statuses are described below.

*Pre-treatment: the patient status is set to 'On-treatment' if the initial result is 'Green'*

**New:** A patient who has never received (any brand of) clozapine. The patient will be registered with ZTAS so that Zaponex treatment may be initiated in due course.

**Interrupted-New:** A patient whose treatment is interrupted for a period that exceeds the maximum treatment break duration as described section [6.1 Treatment break](#).

A patient with the status Interrupted-New has been re-registered with the ZTAS with the intention that Zaponex treatment will be (re-)initiated in due course.

**On-treatment-New:** A patient registered to ZTAS as on-treatment with another brand of clozapine. Zaponex treatment will be initiated in due course.

*The following patient statuses are actively monitored on the ZTAS database:*

**On-treatment:** A patient who is currently treated with Zaponex.

**Discontinued:** A patient who stopped treatment for a reason other than a confirmed 'red' result.

*The discontinuation procedure states that 4 additional weeks of post-treatment monitoring is required at the frequency before treatment stopped.*

*The first 'green' blood result following the status change to discontinued will result in the status being changed from Discontinued to Discontinued-1. The number increases with each subsequent 'green' blood result until 4 additional weeks of monitoring have been completed.*

*After completion of the discontinuation procedure the status will change to **Discontinued-Final** and the patient will no longer be monitored.*

**Non-rechallengeable:** a patient who has experienced an abnormally low blood result classified as a confirmed 'red result', Re-challenge of such a patient with clozapine bears a serious risk and may be life-threatening.

*The Non-Rechallengeable procedure states that daily blood testing of the white blood cell and neutrophil counts are required until the blood results have stabilised in 'green' ranges. After the first 'green' result, 4 additional weeks of post-treatment monitoring is required.*

*The first 'green' blood result following the status change to Non-rechallengeable will result in the status being changed to Non-rechallengeable-1. The number increases with each following weekly 'green' blood result until 4 weeks of monitoring have been completed.*

*After completion of the discontinuation procedure the status will change to **Non-Rechallengeable-Final** and the patient will no longer be monitored.*

*Patients with the following patient statuses are no longer monitored by ZTAS:*

**Interrupted:** A patient whose treatment has been interrupted for a period that exceeds the maximum treatment break duration as described in section [6.1](#). To resume Zaponex treatment, the patient must be re-registered with ZTAS.

**Transferred:** A patient who is no longer treated with Zaponex, having been switched to another manufacturer's brand of clozapine during treatment.

**Deceased:** a patient who has died.

**Discontinued-Final** and **Non-Rechallengeable-Final:** see definitions above