CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022433Orig1s000

ENVIRONMENTAL ASSESSMENT

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmaceutical Science/Immediate Office

Memorandum

Date: March 2, 2010

From: Raanan A. Bloom, Ph.D.
OPS/IO/SRS

To: K. Srinivasachar
ONDQA

Through: Nakissa Sadrieh, Ph.D.
OPS/IO/SRS

Subject: **NDA 22-433:** Ticagrelor (formally known as AZD6140) tablets, 90 mg.
Review of Environmental Assessment

Sponsor: AstraZeneca LP

A. Background

AstraZeneca LP is filing an NDA pursuant to section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for ticagrelor tablets. An environmental assessment (EA) has being submitted pursuant to 21 CFR part 25.

B. Discussion

Executive Summary

This EA supports the NDA for ticagrelor 90 mg tablets for the prevention of thrombotic events in patients with acute coronary syndromes. Ticagrelor is a platelet aggregation inhibitor. The EA was prepared in accordance with 21 CFR Part 25 by AstraZeneca LP.

The sponsor estimates an EIC of (b) (4), used in the United States. The EA is compiled in accordance with FDA 'Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications' CDER, CBER, FDA July 1998.

The sponsor used chronic ecotoxicology data to estimate a Predicted No Effect Concentration (PNEC) in the environment. This is compared to the Predicted Environmental Concentration (PEC); the resulting ratio was determined to be (b) (4), concluding that ticagrelor residues in the environment do not pose an environmental concern based on the predicted amount of ticagrelor residues expected to enter the environment by year 5 after approval.

C. Environmental Assessment Review

1. **Date:** 26 June 2009
2. **Applicant:** AstraZeneca LP
3. **Address:** 800 Concord Pike, PO Box 8355, Wilmington, DE 19803-8355
4. **Proposed Action:** Prevention of thrombotic events in patients with acute coronary syndromes.

5. Identification of Chemicals

(i) Established Name: Ticagrelor (formerly known as AZD6140)
(ii) Brand/Proprietary Name/Tradename: TBD
(iii) Chemical Name: (1S,2S,3R,5S)-3-[7-{[(1R,2S)-2-(3,4-Difluorophenyl)cyclopropyl]amino}-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol
(iv) Chemical Abstract Registration Number: 274693-27-5
(v) Molecular Formula: $C_{23}H_{28}F_2N_6O_4S$
(vi) Molecular Weight: 522.57
(vii) Chemical Structure: see EA

6. Environmental Fate Characterization

Physical/Chemical Values

Water solubility:
5.3 mg/L at pH 5
3.5 mg/L at pH 7
11 mg/L at pH 9

Dissociation constants (pKa)
Ticagrelor exhibits no pKa within the physiological range (pH 1-8).

Octanol/Water Partition Coefficient
log D_{ow} > 4.02 at pH 5, 7 and 9

Vapor Pressure
Not determined. Ticagrelor is a solid and hence its v.p. is assumed to be very low ($<10^{-6}$ Pa).

Sorption/Desorption

$K_{d(ads)}$ was 1571
$K_{oc} = K_{d(ads)} / 0.37 = 1571 / 0.37 = 4246$

Bioconcentration in rainbow trout (*Oncorhynchus mykiss*)
Due to the potential for ticagrelor to bioaccumulate (log D_{ow} value > 4.02), the bioconcentration in *O. mykiss* was assessed according to OECD test guideline 305 at 1.0 µg/L. At days 14 and 28, fish were sampled and kinetic bioconcentration factors (BCFs) were calculated to be 2.91 and 6.36, respectively. These values indicate that ticagrelor is not bioaccumulative.

Environmental Depletion Mechanisms

Biodegradation

The aerobic biodegradation of ticagrelor was assessed according to OECD guideline 301F. In this test, aerobic microorganisms from a sewage treatment system are used to investigate the potential to readily degrade a substance. The results showed that ticagrelor is not readily biodegradable; <5% degradation after 28 days.

Hydrolysis – preliminary study

The stability of ticagrelor in aqueous buffer solutions was assessed according to the OECD test guideline 111. The extent of hydrolysis after 5 days at 50°C was 18% at pH 5, and <10% at pH 7 and 9. These data indicate that ticagrelor is hydrolytically stable, with an estimated half-life of ≥1 year at 25°C.

Environmental Fate

The use of ticagrelor is predicted to result in parent compound and metabolites entering the environment. The main part of the dose is excreted via feces (approx. 60%), whereas approximately 27% is excreted via urine. The main part of the dose is excreted as metabolites, whereas approximately 27% is excreted as the parent compound. Based on the physico-chemical properties of ticagrelor (water solubility =3.5 mg/L, Koc sludge = 4246 and vapour pressure $<10^{-6}$ Pa) it is predicted that most of the active moiety will be expected to partition into the aqueous phase during wastewater treatment. There is no evidence to suggest that biodegradation will be significant. The aqueous streams containing ticagrelor will then subsequently be passed to the aquatic environment. When estimating the Expected Introduction Concentration (EIC), it is assumed that all ticagrelor ends up in the aquatic environment in potentially active forms, which is regarded as the worst case scenario. In the aquatic environment, ticagrelor is not predicted to be hydrolytically degraded. However, there is evidence that the substance will partition into, and degrade within, aquatic sediments. Ticagrelor is not predicted to bioaccumulate in aquatic organisms.

7. Environmental Effects (Ecological Toxicity)

ADME data is presented in the EA.

The following ecotoxicity effects studies (see appended Table, below) were conducted in accordance with OECD guidelines and submitted as appendices to the EA. Based on the results, the most sensitive species to ticagrelor is the copepod, *Daphnia magna*.

Result from the microbial inhibition test indicates that the drug substance does not inhibit respiration of activated sludge microorganisms. Ticagrelor is not thought to disrupt wastewater treatment processes. Furthermore, as the bioconcentration factor is very low, ticagrelor it is not likely to bioaccumulate in aquatic organisms..

8. Cumulative Environmental Fate and Effects

No other NDAs or ANDAs are approved for AZD6140 or ticagrelor: the estimates contained above include cumulative effects for this compound.

9. Mitigation Measures and Alternatives

Since no adverse environmental impact is expected, no mitigation methods are addressed.

10. Literature Reviewed

Findings: No published, peer-reviewed environmental or ecotoxicology literature was found.

11. Comments and Conclusions

Chronic data are available for fish, *D. magna* and microalga: however, the most sensitive endpoint was established in the *D. magna* acute toxicity study (conducted as part of the acute toxicity base set of tests) and therefore, as desceibed in the FDA guidance, a Tier 2 assessment factor of 100 was used for determining if sufficient safety margins exist to preclude the need for additional studies.

D. magna 48 h EC_{50} = 1.4 mg/L; EIC = (b) (4) AF = 100

EC_{50}/EIC = 1400/ (b) (4) >100; no effects were observed at the Maximum Expected Environmental Concentration (MEEC). No further testing is needed.

Based on an evaluation of the information provided in this EA and previous EAs, in FDA guidance, and on the scientific validity of the "no effects" conclusions of the EA, no significant adverse environmental impacts are expected from the approval of ticagrelor.

A Finding of No Significant Impact (FONSI) is recommended.

Ticagrelor – Ecotoxicity studies

Study	Results
Activated sludge, respiration inhibition test, OECD 209	• 3 h No observed effect concentration (NOEC) = 100 mg/L • 3 h Effect Concentration $(EC)_{50}$ >100 mg/L
Toxicity to the freshwater green alga *Selenastrum capricornutum*, OECD 201	• 72 h $NOEC_{growth\ rate}$ = 0.82 mg/L • 72 h Lowest Observed Effect Concentration $(LOEC)_{growth\ rate}$ = 1.9 mg/L • 72 h $NOEC_{biomass}$ = 0.82 mg/L • 72 h $LOEC_{biomass}$ = 1.9 mg/L
Acute toxicity to *Daphnia magna*, OECD 202	• 48 h NOEC = 0.68 mg/L • 48 h EC_{50} = 1.4 mg/L
Chronic toxicity to *Daphnia magna*, OECD 211	• 21 d NOEC = 0.53 mg/L and; • 21 d LOEC = 1.7 mg/L based on length • No biologically relevant statistical differences on survival and reproduction
Acute toxicity to rainbow trout, *Oncorhynchus mykiss,* OECD 203	• 96 h NOEC >2.7 mg/L
Fish early-life stage toxicity with fathead minnow, *Pimephales promelas* OECD 210	• 32 d NOEC = 1.8 mg/L based on hatch, survival, length and dry weight • 32 d LOEC >1.8 mg/L
Toxicity to *Chironomus riparius*, OECD guideline 218	• 28 d NOEC = 30 mg/kg dry sediment and; • 28 d LOEC > 30 mg/kg dry sediment

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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/s/

RAANAN A BLOOM
03/05/2010
EA Review

NAKISSA SADRIEH
03/05/2010

Environmental Assessment
Finding of No Significant Impact

NDA 22-433:
Ticagrelor tablets, 90 mg for the prevention of thrombotic events in patients with acute coronary syndromes

Food and Drug Administration
Center for Drug Evaluation and Research

March 2, 2010

FINDING OF NO SIGNIFICANT IMPACT

NDA 22-433

Ticagrelor tablets, 90 mg, for the prevention of thrombotic events in patients with acute coronary syndromes

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. The Food and Drug Administration (FDA) is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of the regulatory process.

NDA 22-433 requests approval for ticagrelor tablets, 90 mg, for the prevention of thrombotic events in patients with acute coronary syndromes. In support of its application, Astra Zeneca LP prepared an environmental assessment (EA; attached) in accordance with 21 CFR Part 25, which evaluates the potential environmental impacts of Ticagrelor.

The Food and Drug Administration, Center for Drug Evaluation and Research, has carefully considered the potential environmental impact due to approval of this application and has concluded that this action is not expected to have a significant effect on the human environment. Therefore, an environmental impact statement will not be prepared.

PREPARED BY:

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Office of Pharmaceutical Science

Attachment: 26 June 2009, Environmental Assessment

AstraZeneca

Environmental Assessment	
Drug Substance	Ticagrelor
Document No.	CV.000-508-987
Date	22 July 2009

Environmental Assessment of Ticagrelor

Author: Gisela Holm, PhD
Ecotoxicologist
Essential SHE, Operations

TABLE OF CONTENTS PAGE

1. DATE

26 June 2009

2. NAME OF APPLICANT/PETITIONER

AstraZeneca LP

3. ADDRESS

AstraZeneca LP
1800 Concord Pike
PO Box 8355
Wilmington, DE 19803-8355

4. DESCRIPTION OF PROPOSED ACTION

4.1 Requested approval

AstraZeneca LP is filing an NDA pursuant to section 505(b)(1) of the Federal Food, Drug and Cosmetic Act for ticagrelor (formally known as AZD6140) tablets. An environmental assessment (EA) is being submitted pursuant to 21 CFR part 25. The EA is compiled in accordance with 'Guidance for Industry, Environmental Assessment of Human Drug and Biologics Applications' CDER, CBER, FDA July 1998.

4.2 Need for action

This new drug application provides for the use of ticagrelor tablets, 90 mg, for the prevention of thrombotic events in patients with acute coronary syndromes.

4.3 Locations of use

The product is expected to be used in an outpatient/hospital setting, long-term care facility, clinic, doctor's office, or home. The proposed distribution of the product is to be dispensed from a retail or hospital pharmacy setting.

4.4 Disposal sites

Empty or partially empty packages from U.S. households, hospitals, pharmacies or clinics will be disposed of according to hospital, pharmacy, or clinic procedures.

5. IDENTIFICATION OF SUBSTANCES THAT ARE THE SUBJECT OF THE PROPOSED ACTION

See 3.2.S.1.1 Nomenclature and 3.2.S.1.2 Structure in Module 3.

5.1 Nomenclature

5.1.1 Established name (U.S. Adopted name - USAN)

Ticagrelor (formerly known as AZD6140)

5.1.2 Brand/Proprietary name/tradename

Not yet decided.

5.1.3 Chemical names

5.1.3.1 Systematic chemical name (IUPAC)

(1*S*,2*S*,3*R*,5*S*)-3-[7-{[(1*R*,2*S*)-2-(3,4-Difluorophenyl)cyclopropyl]amino}-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol

5.2 Chemical abstracts service (CAS) registration number

274693-27-5

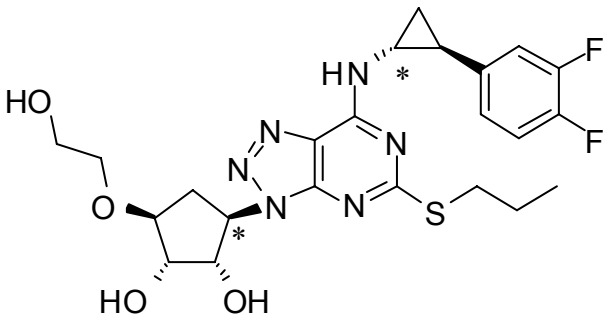
5.3 Molecular formula

$C_{23}H_{28}F_2N_6O_4S$

5.4 Molecular weight

522.57

5.5 Structural (graphic) formula



In the structural formula above, all chiral centres are in the *S*-configuration except those marked * which are in the *R*-configuration.

6. ENVIRONMENTAL ISSUES

6.1 Environmental Fate of Released Substances

6.1.1 Identification of Substances of Interest

Please see Figure 1 for a summary of the proposed *in vivo* metabolic pathways of ticagrelor (AZD6140) in man.

After oral administration, ticagrelor is metabolised and excreted via urine (27% of administered dose and to a larger extent via faeces (58% of administered dose (Appendix 1 – **Confidential**). The main part of the dose is excreted as metabolites, whereas approximately 27% is excreted as the parent compound (ticagrelor) in faeces. Only approximately 0.02% of the dose is excreted as the parent compound in urine. The main metabolite, AR-C124910XX, is excreted almost solely via faeces (approximately 22% of given dose) (Appendix 2 - Confidential) and only to a minor extent via urine (approximately 0.04%). The main metabolite excreted via urine is AR-C133913XX (approximately 9% of given dose) (Appendix 2 - **Confidential**). A major metabolic pathway is *via* oxidative loss of the hydroxyethyl side-chain to form AR-C124910XX. A second significant oxidative pathway leads to the N-dealkylation of AZD6140 forming AR-C1339139XX. The remaining part of the administered dose is excreted as minor metabolites (< 3% per metabolite). Three of the minor metabolites are formed via glucuronidation of AZD6140, AR-C124910XX and AR-C1339139XX, respectively, and are excreted renally. In addition, some of the remaining metabolites are formed via hydroxylation.

The main metabolite, AR-C124910XX, has a comparable pharmacology profile against the $P2Y_{12}$ receptor as ticagrelor. With regard to the rest of the metabolites, they are regarded as pharmacologically inactive.

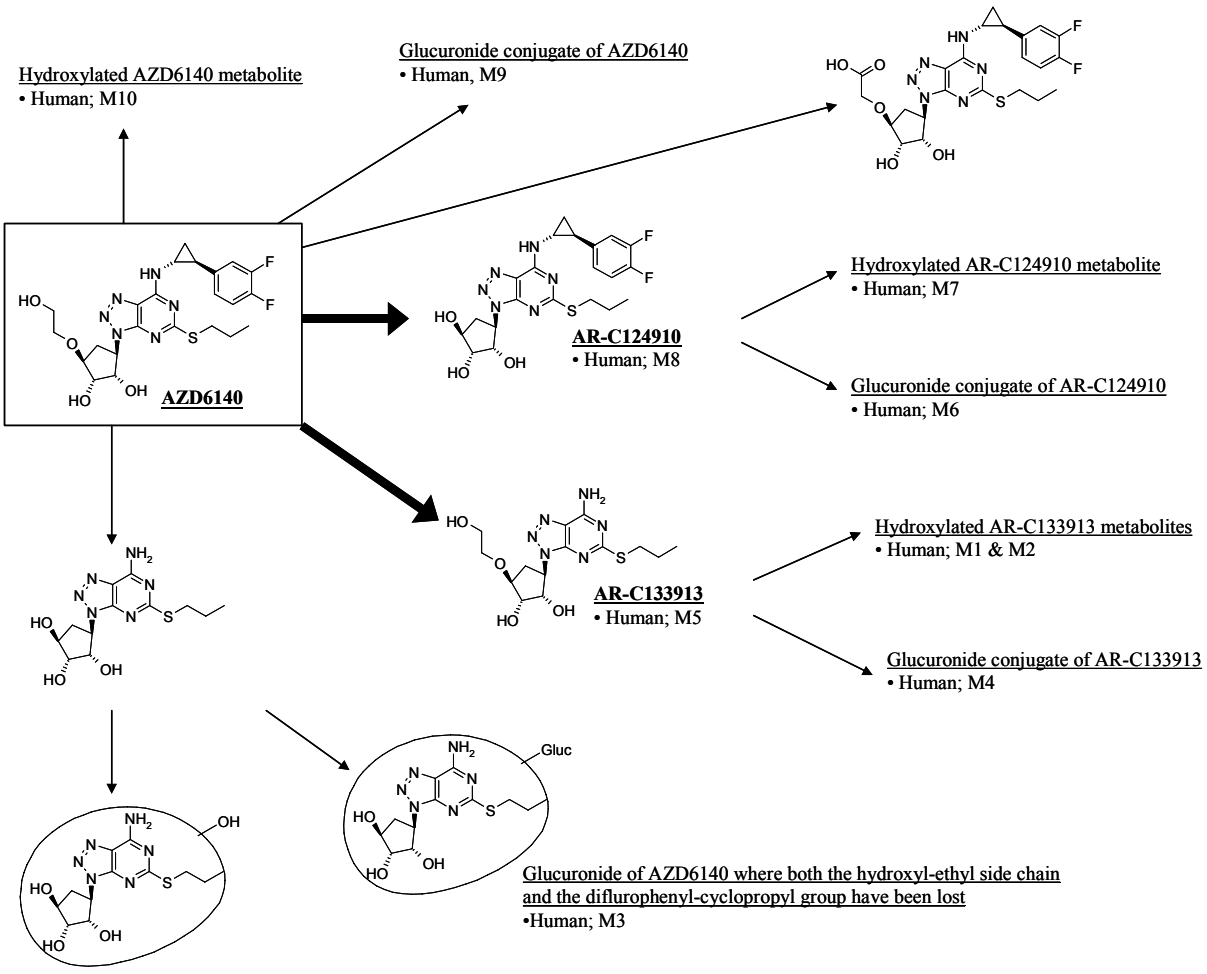


Figure 1. Proposed *in vivo* metabolic pathways of ticagrelor (AZD6140) in man.

6.1.2 Physical and Chemical Characterization

Water solubility

See Appendix 3 – **Confidential**..

5.3 mg/L at pH 5
3.5 mg/L at pH 7
11 mg/L at pH 9

Dissociation constants (pKa)

Ticagrelor exhibits no pKa within the physiological range (pH 1-8).

Octanol/Water Partition Coefficient

log D_{ow} > 4.02 at pH 5, 7 and 9 (Appendix 4 – **Confidential**)

Bioconcentration in rainbow trout (*Oncorhynchus mykiss)*

Due to the potential for ticagrelor to bioaccumulate, according to the log D_{ow} value, the bioconcentration in *O. mykiss* was assessed according to the OECD 305 Test Guideline (Appendix 5 - **Confidential**) at 1.0 µg/L.

At Days 14 and 28, fish were sampled and kinetic bioconcentration factors (BCFs) were calculated to be 2.91 and 6.36 respectively. These figures indicate that ticagrelor is not bioaccumulative.

Vapour pressure

Not determined. Ticagrelor is a solid and hence its vapour pressure is assumed to be very low (<10^{-6} Pa).

6.1.3 Environmental Depletion Mechanisms

Biodegradation

The aerobic biodegradation of ticagrelor was assessed according to guideline OECD 301F (Appendix 6 - **Confidential**). In this test, aerobic microorganisms from a sewage treatment works are used to investigate their potential to readily degrade a substance. The results showed that ticagrelor is not readily biodegradable; <5% degradation after 28 days.

Hydrolysis – preliminary study

The stability of ticagrelor in aqueous buffer solutions was assessed according to the OECD test guideline 111 (Appendix 7 – **Confidential**). The extent of hydrolysis after 5 days at 50°C was 18% at pH 5, and <10% at pH 7 and 9. These data indicate that ticagrelor is hydrolytically stable, with an estimated half-life of ≥1 year at 25°C.

Adsorption to sludge

The estimation of the adsorption coefficient to sludge ($K_{d(ads)}$) was assessed according to the OPPTS guideline 835.1110 (Appendix 8 - **Confidential**). The $K_{d(ads)}$ was 1571 and can be used to estimate the likely removal of ticagrelor by adsorption, during sewage treatment. The content of carbon in sewage is 37% according to the Technical Guidance Document on Risk Assessments, therefore the equivalent K_{oc} value would be:

$K_{oc} = K_{d(ads)} / 0.37 = 1571 / 0.37 = 4246$

Aerobic transformation in aquatic sediment systems

The aerobic transformation in aquatic sediment systems was assessed according to the OECD guideline 308 (Appendix 9 - **Confidential**). Two different sediments were used, one with high organic matter (HOM) and one with low organic matter (LOM) content. Radiolabelled test substance was dosed into the overlying water and the subsequent dissipation from the water phase, and partitioning and/or degradation in the sediment, was observed over a 99 day test period

In both the high and low organic matter test vessels rapid dissipation of [^{14}C]AZD6140 from the overlying water was observed, with very low concentrations measured from day 14 onwards. A maximum concentration of [^{14}C]AZD6140 was observed in the high and low sediment extracts on day 14 (18 and 43% of the applied radioactivity, respectively), which died away to <10% of the applied radioactivity by the end of the study.

The results can be summarised as follows:

	Compartment	**Simple first order (SFO) dissipation half-life (d)**
High organic matter sediment	Overlying water	2.20
	Sediment extract	30.9
	Total system	11.3
Low organic matter sediment	Overlying water	2.87
	Sediment extract	22.8
	Total system	19.6

Overall, the evidence from this study suggests that ticagrelor will not be persistent in the aquatic environment.

6.1.4 Environmental Concentrations

The Expected Introduction Concentration (EIC) is based on the forecasted amount of ticagrelor to be produced for direct use in the US. See Appendix 10 – **Confidential.**

6.1.4.1 Summary

The use of ticagrelor is predicted to result in parent compound and metabolites entering the environment. The main part of the dose is excreted *via* faeces (approx. 60%), whereas approximately 27% is excreted *via* urine. The main part of the dose is excreted as metabolites, whereas approximately 27% is excreted as the parent compound.

Based on the physico-chemical properties of ticagrelor (water solubility =3.5 mg/L, K_{oc} sludge = 4246 and vapour pressure $<10^{-6}$ Pa) it is predicted that most of the active moiety (ticagrelor) will be partitioned into the aqueous phase during wastewater treatment. There is no evidence to suggest that biodegradation will be significant. The aqueous streams containing ticagrelor will then subsequently be passed to the aquatic environment. When estimating the Expected Introduction Concentration (EIC), it is assumed that all ticagrelor ends up in the aquatic environment in potentially active forms, which is regarded as worst case.

In the aquatic environment, ticagrelor is not predicted to be hydrolytically degraded. However, there is evidence that the substance will partition into, and degrade within, aquatic sediments. Ticagrelor is not predicted to bioaccumulate in aquatic organisms.

6.2 Environmental Effects of Released Substances

The following ecotoxicological studies have been performed with ticagrelor:

Table 3. Ticagrelor – Ecotoxicity studies

Study	Results
Activated sludge, respiration inhibition test, OECD 209 (Appendix 11 - **Confidential**)	• 3 h No observed effect concentration (NOEC) = 100 mg/L • 3 h Effect Concentration $(EC)_{50}$ >100 mg/L
Toxicity to the freshwater green alga *Selenastrum capricornutum*, OECD 201 (Appendix 12 - **Confidential**)	• 72 h $NOEC_{growth\ rate}$ = 0.82 mg/L • 72 h Lowest Observed Effect Concentration $(LOEC)_{growth\ rate}$ = 1.9 mg/L • 72 h $NOEC_{biomass}$ = 0.82 mg/L • 72 h $LOEC_{biomass}$ = 1.9 mg/L
Acute toxicity to *Daphnia magna*, OECD 202 (Appendix 13 - **Confidential**)	• 48 h NOEC = 0.68 mg/L • 48 h EC_{50} = 1.4 mg/L
Chronic toxicity to *Daphnia magna*, OECD 211 (Appendix 14 - **Confidential**)	• 21 d NOEC = 0.53 mg/L and; • 21 d LOEC = 1.7 mg/L based on length • No biologically relevant statistical differences on survival and reproduction
Acute toxicity to rainbow trout, *Oncorhynchus mykiss,* OECD 203 (Appendix 15 - **Confidential**)	• 96 h NOEC >2.7 mg/L
Fish early-life stage toxicity with fathead minnow, *Pimephales promelas* OECD 210 (Appendix 16 - **Confidential**)	• 32 d NOEC = 1.8 mg/L based on hatch, survival, length and dry weight • 32 d LOEC >1.8 mg/L
Toxicity to *Chironomus riparius*, OECD guideline 218 (Appendix 17 - **Confidential**).	• 28 d NOEC = 30 mg/kg dry sediment and; • 28 d LOEC > 30 mg/kg dry sediment

Based on the results above, the most sensitive species to ticagrelor is the copepod *Daphnia magna.*

6.2.1 Tiered assessment

No rapid, complete depletion mechanism has been identified for ticagrelor. However, the result from the microbial inhibition test above indicates that the drug substance does not inhibit respiration of activated sludge microorganisms. Therefore, ticagrelor is not thought to disrupt wastewater treatment processes. Furthermore, as the bioconcentration factor is very low (see 6.1.2 Physical and Chemical Characterization), it is not likely to bioaccumulate in aquatic organisms, and Tier 1 is justified.

Chronic data are available for fish, *D. magna* and microalga, however, the most sensitive endpoint was established in the *D. magna* acute toxicity study and therefore, a Tier 2 assessment has been undertaken on a precautionary basis, which means an assessment factor of 100 is justified.

D. magna 48 h EC_{50} = 1.4 mg/L

EC_{50}/EIC (Appendix 10 - **Confidential**) = 1400/EIC >100 (assessment factor), and no effects were observed at the Maximum Expected Environmental Concentration (MEEC), i.e. no further testing is needed.

6.2.2 Summary

The use of ticagrelor is predicted to result in parent compound (approx. 27%) and metabolites entering the environment. It is predicted that most of the active moiety (ticagrelor) will be partitioned into the aqueous phase during wastewater treatment. There is no evidence to suggest that biodegradation will be significant.

In the aquatic environment, ticagrelor is not predicted to be hydrolytically degraded. However, there is evidence that the substance will partition into, and degrade within, aquatic sediments. Ticagrelor is not predicted to bioaccumulate in aquatic organisms.

When estimating the EIC, it is assumed that all ticagrelor ends up in the aquatic environment in potentially active forms, which is regarded as worst case. Comparing the EIC with the EC_{50} from the most sensitive species (*D. magna*) using an assessment factor of 100 (Tier 2) gives:

EC_{50}/EIC = 1400/ EIC >100 (assessment factor)

In conclusion, since the ratio of the EC_{50} for the most sensitive of the acute toxicity test organisms to the expected introduction concentration is over one order of magnitude greater than the assessment factor, and no effects were observed at MEEC, no adverse environmental effects are anticipated as a consequence of the use of ticagrelor.

7. MITIGATION MEASURES

No adverse environmental effects are anticipated due to the use of ticagrelor. Therefore, no mitigation measures are needed.

8. ALTERNATIVES TO THE PROPOSED ACTION

No potential adverse environmental effects have been identified for the proposed action. Therefore, no alternatives to the proposed action will be presented.

9. LIST OF PREPARERS

Gisela Holm, Ecotoxicologist, Senior SHE Specialist, AstraZeneca, PhD Stockholm University, 20 years of experience in environmental research and consulting.

Persons consulted:

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Hans van Giezen, AstraZeneca R&D Mölndal, Sweden
Britt-Marie Emanuelsson, AstraZeneca R&D Mölndal, Sweden
Judith Prosser, Regulatory Affairs, AstraZeneca Pharmaceuticals, USA
Keith Purdy, Project Manager, PAR&D, AstraZeneca, R&D Charnwood, UK
Joshua Prince, Commercial Operations, AstraZeneca Pharmaceuticals, USA

Testing laboratory:

Brixham Environmental Laboratory, AstraZeneca, Brixham, UK

10. APPENDICES

10.1 Nonconfidential Appendices

10.1.1 Data Summary Table

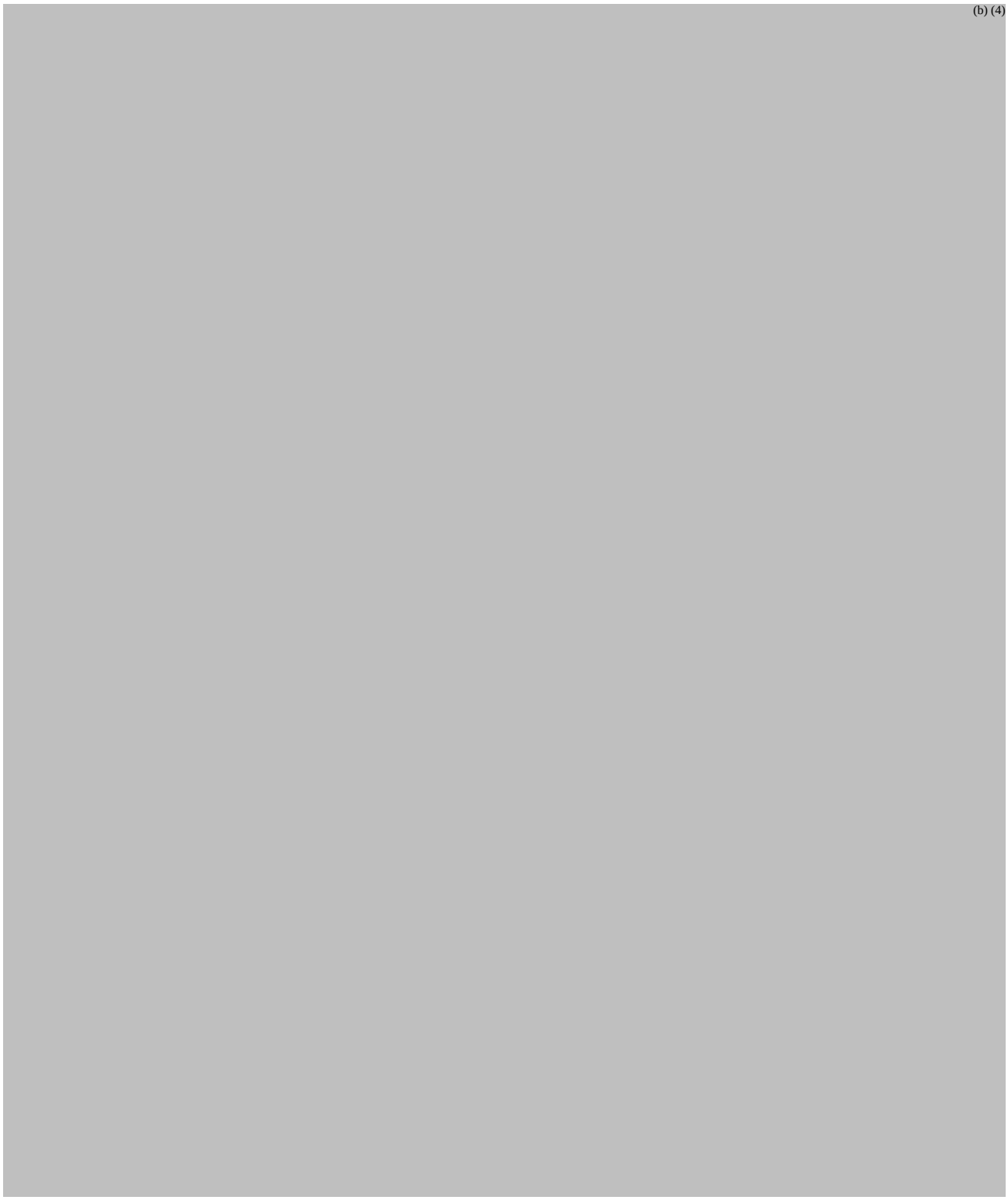
DATA SUMMARY TABLE FOR TICAGRELOR	
PHYSICAL/CHEMICAL CHARACTERIZATION	
Water Solubility	5.3 mg/L at pH 5 3.5 mg/L at pH 7 11 mg/L at pH 9
Dissociation Constants	No pKa within the physiological range (pH 1-8).
Log Octanol/Water Partition Coefficient (log D_{ow})	log D_{ow} > 4.02 at pH 5, 7 and 9 BCF = 6.36 at Day 28
Vapour Pressure or Henry's Law Constant	No data
Adsorption to sludge	K_{oc} = 4246
DEPLETION MECHANISMS	
Hydrolysis (preliminary study)	t½ at 25°C ≥ 1 year
Aerobic Biodegradation	Not readily biodegradable (<5% after 28 d)
Transformation in aquatic sediment systems	Dissipation half-life as: DT50 in HOM, total system = 11.3 days DT50 in LOM, total system = 19.6 days Evidence suggest that the substance will not be persistent in the aquatic environment.
Metabolism	27% of the does excreted as parent molecule and the rest as metabolites

ENVIRONMENTAL EFFECTS	
Microbial Inhibition	3h EC_{50} >100 mg/L 3h NOEC = 100 mg/L
Acute toxicity	**Rainbow trout** (*Oncorhynchus mykiss*) 96 h EC_{50} > water solubility (approx. 2.7 mg/L) 96 h NOEC > water solubility (approx. 2.7 mg/L) **Water flea** (*Daphnia magna*) 48 h EC_{50} = 1.4 mg/L 48 h NOEC = 0.68 mg/L
Chronic Toxicity	**Green alga** (*Selenastrum capricornutum*) 72 h $NOEC_{growth\ rate}$ = 0.82 mg/L 72 h $LOEC_{growth\ rate}$ = 1.9 mg/L 72 h $NOEC_{biomass}$ = 0.82 mg/L 72 h $LOEC_{biomass}$ = 1.9 mg/L **Water flea** (*Daphnia magna*) 21 d NOEC = 0.53 mg/L 21 d LOEC = 1.7 mg/L **Fathead minnow** (*Pimephales promelas*) 32 d NOEC = 1.8 mg/L 32 d LOEC >1.8 mg/L

10.2 Confidential Appendices

(b) (4)

(b) (4)



Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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03/07/2010